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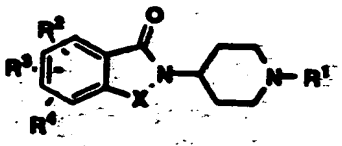
(54) Title: INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND METHOD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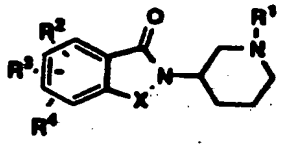
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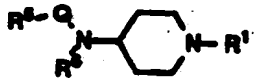
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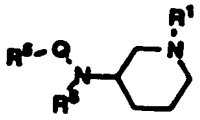
(d)

(57) Abstract

Compounds are provided which inhibit microsomal triglyceride transfer protein and thus are useful for lowering serum lipids and treating atherosclerosis and related diseases. The compounds have the structure (a, b, c or d) wherein R^1 to R^6, Q, and X are as defined herein.

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INHIBITORS OF MICROSOMAL TRIGLYCERIDE TRANSFER PROTEIN AND METHOD

This invention relates to novel compounds which inhibit microsomal triglyceride transfer protein, and to methods for decreasing serum lipids and treating atherosclerosis employing such compounds.

The microsomal triglyceride transfer protein (MTP) catalyzes the transport of triglyceride (TG), cholesteryl ester (CE), and phosphatidylcholine (PC) between small unilamellar vesicles (SUV). Wetterau & Zilversmit, Chem. Phys. Lipids 38, 205-22 (1985). When transfer rates are expressed as the percent of the donor lipid transferred per time, MTP expresses a distinct preference for neutral lipid transport (TG and CE), relative to phospholipid transport. The protein from bovine liver has been isolated and characterized. Wetterau & Zilversmit, Chem. Phys. Lipids 38, 205-22 (1985). Polyacrylamide gel electrophoresis (PAGE) analysis of the purified protein suggests that the transfer protein is a complex of two subunits of apparent molecular weights 58,000 and 88,000, since a single band was present when purified MTP was electrophoresed under nondenaturing condition, while two bands of apparent molecular weights 58,000 and 88,000 were identified when electrophoresis was performed in the presence of sodium dodecyl sulfate (SDS). These two polypeptides are hereinafter referred to as 58 kDa and 88 kDa, respectively, or the 58 kDa and the 88 kDa component of MTP, respectively, or the low molecular weight

subunit and the high molecular weight subunit of MTP, respectively.

Characterization of the 58,000 molecular weight component of bovine MTP indicates that it is the previously characterized multifunctional protein, protein disulfide isomerase (PDI). Wetterau et al., J. Biol. Chem. 265, 9800-7 (1990). The presence of PDI in the transfer protein is supported by evidence showing that (1) the amino terminal 25 amino acids of the bovine 58,000 kDa component of MTP is identical to that of bovine PDI, and (2) disulfide isomerase activity was expressed by bovine MTP following the dissociation of the 58 kDa - 88 kDa protein complex. In addition, antibodies raised against bovine PDI, a protein which by itself has no TG transfer activity, were able to immunoprecipitate bovine TG transfer activity from a solution containing purified bovine MTP.

PDI normally plays a role in the folding and assembly of newly synthesized disulfide bonded proteins within the lumen of the endoplasmic reticulum. Bulleid & Freedman, Nature 335, 649-51 (1988). It catalyzes the proper pairing of cysteine residues into disulfide bonds, thus catalyzing the proper folding of disulfide bonded proteins. In addition, PDI has been reported to be identical to the beta subunit of human prolyl 4-hydroxylase. Koivu et al., J. Biol. Chem. 262, 6447-9 (1987). The role of PDI in the bovine transfer protein is not clear. It does appear to be an essential component of the transfer protein as dissociation of PDI from the 88 kDa component of bovine MTP by either low concentrations of a denaturant (guanidine HCl), a chaotropic agent (sodium perchlorate), or a

nondenaturing detergent (octyl glucoside) results in a loss of transfer activity. Wetterau et al., Biochemistry 30, 9728-35 (1991). Isolated bovine PDI has no apparent lipid transfer activity, suggesting that either the 88 kDa polypeptide is the transfer protein or that it confers transfer activity to the protein complex.

The tissue and subcellular distribution of MTP activity in rats has been investigated. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). Lipid transfer activity was found in liver and intestine. Little or no transfer activity was found in plasma, brain, heart, or kidney. Within the liver, MTP was a soluble protein located within the lumen of the microsomal fraction. Approximately equal concentrations were found in the smooth and rough microsomes.

Abetalipoproteinemia is an autosomal recessive disease characterized by a virtual absence of plasma lipoproteins which contain apolipoprotein B (apoB). Kane & Havel in The Metabolic Basis of Inherited Disease, Sixth edition, 1139-64 (1989). Plasma TG levels may be as low as a few mg/dL, and they fail to rise after fat ingestion. Plasma cholesterol levels are often only 20-45 mg/dL. These abnormalities are the result of a genetic defect in the assembly and/or secretion of very low density lipoproteins (VLDL) in the liver and chylomicrons in the intestine. The molecular basis for this defect has not been previously determined. In subjects examined, triglyceride, phospholipid, and cholesterol synthesis appear normal. At autopsy, subjects are free of atherosclerosis. Schaefer et al., Clin. Chem. 34, B9-12 (1988). A link between the apoB gene and

abetalipoproteinemia has been excluded in several families. Talmud et al., J. Clin. Invest. 82, 1803-6 (1988) and Huang et al., Am. J. Hum. Genet. 46, 1141-8 (1990).

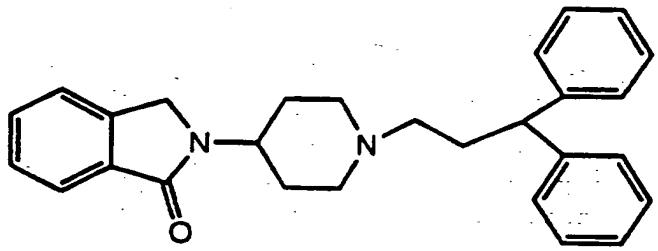
Subjects with abetalipoproteinemia are afflicted with numerous maladies. Kane & Havel, supra. Subjects have fat malabsorption and TG accumulation in their enterocytes and hepatocytes. Due to the absence of TG-rich plasma lipoproteins, there is a defect in the transport of fat-soluble vitamins such as vitamin E. This results in acanthocytosis of erythrocytes, spinocerebellar ataxia with degeneration of the fasciculus cuneatus and gracilis, peripheral neuropathy, degenerative pigmentary retinopathy, and ceroid myopathy. Treatment of abetalipoproteinemic subjects includes dietary restriction of fat intake and dietary supplementation with vitamins A, E and K.

In vitro, MTP catalyzes the transport of lipid molecules between phospholipid membranes. Presumably, it plays a similar role in vivo, and thus plays some role in lipid metabolism. The subcellular (lumen of the microsomal fraction) and tissue distribution (liver and intestine) of MTP have led to speculation that it plays a role in the assembly of plasma lipoproteins, as these are the sites of plasma lipoprotein assembly. Wetterau & Zilversmit, Biochem. Biophys. Acta 875, 610-7 (1986). The ability of MTP to catalyze the transport of TG between membranes is consistent with this hypothesis, and suggests that MTP may catalyze the transport of TG from its site of synthesis in the endoplasmic reticulum (ER) membrane to nascent lipoprotein particles within the lumen of the ER.

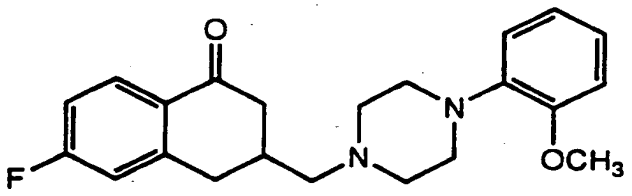
Olofsson and colleagues have studied lipoprotein assembly in HepG2 cells. Bostrom et al., J. Biol. Chem. 263, 4434-42 (1988). Their results suggest small precursor lipoproteins become larger with time. This would be consistent with the addition or transfer of lipid molecules to nascent lipoproteins as they are assembled. MTP may play a role in this process. In support of this hypothesis, Howell and Palade, J. Cell Biol. 92, 833-45 (1982), isolated nascent lipoproteins from the hepatic Golgi fraction of rat liver. There was a spectrum of sizes of particles present with varying lipid and protein compositions. Particles of high density lipoprotein (HDL) density, yet containing apoB, were found. Higgins and Hutson, J. Lipid Res. 25, 1295-1305 (1984), reported lipoproteins isolated from Golgi were consistently larger than those from the endoplasmic reticulum, again suggesting the assembly of lipoproteins is a progressive event.

Recent reports (Science, Vol. 258, page 999, 1992; D. Sharp et. al., Nature, Vol. 365, page 65, 1993) demonstrate that the defect causing abetalipoproteinemia is in the MTP gene, and as a result, the MTP protein. Individuals with abetalipoproteinemia have no MTP activity, as a result of mutations in the MTP gene, some of which have been characterized. These results indicate that MTP is required for the synthesis of apoB containing lipoproteins, such as VLDL, the precursor to LDL. It therefore follows that inhibitors of MTP would inhibit the synthesis of VLDL and LDL, thereby lowering VLDL levels, LDL levels, cholesterol levels, and triglyceride levels in animals and man.

Canadian Patent Application No. 2,091,102 published March 2, 1994 (corresponding to U.S. application Serial No. 117,362, filed September 3, 1993 (file DC21b)) reports MTP inhibitors which also block the production of apoB containing lipoproteins in a human hepatic cell line (HepG2 cells). This provides further support for the proposal that an MTP inhibitor would lower apoB containing lipoprotein and lipid levels in vivo. This Canadian patent application discloses a method for identifying the MTP inhibitors



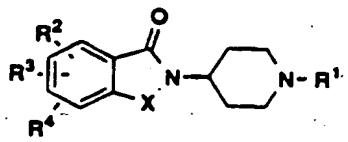
which has the name 2-[1-(3, 3-diphenylpropyl)-4-piperidinyl]-2, 3-dihydro-3-oxo-1H-isoindole hydrochloride and



which has the name 1-[3-(6-fluoro-1-tetralanyl)methyl]-4-O-methoxyphenyl piperazine

In accordance with the present invention, novel compounds are provided which are inhibitors of MTP and have the structure

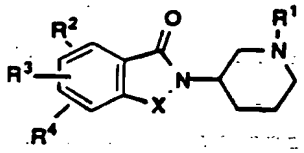
I



;

or

Ii



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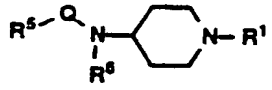
or

II



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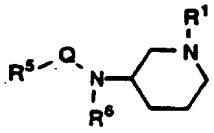
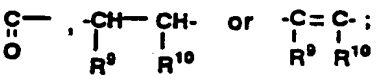
IIi



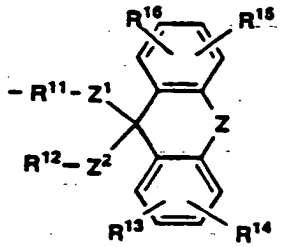
;

where Q is  or  ;

X is: CHR^8,  ;

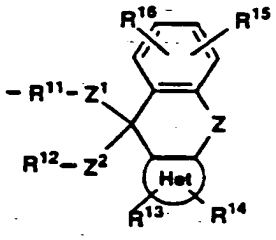
R^8, R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R^1 is a fluorenyl-type group of the structure



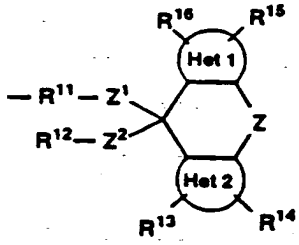
B

or



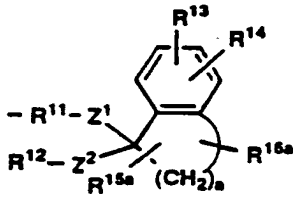
C

or



D ; or

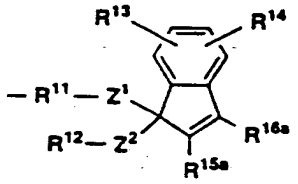
R^1 is an indenyl-type group of the structure



E

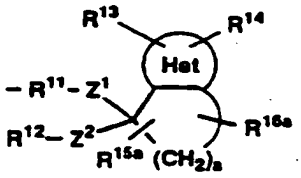
(a = 2,3 or 4)

or



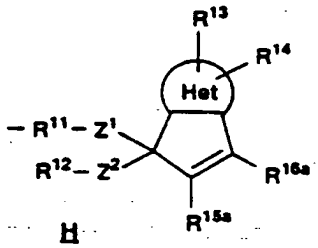
or

F



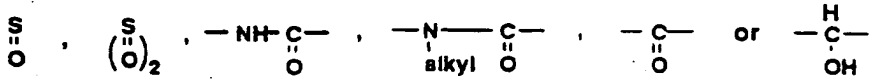
G

or



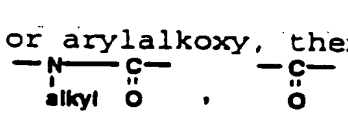
H ;

Z^1 and Z^2 are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond;

R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms, arylene (for example ), or mixed arylene-alkylene (for example ) where n is 1 to 6;

R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroarylalkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl; with the provisos that (1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is  or a bond;

and (2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is a bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene of from 1 to 5 carbon atoms;

R^{13}, R^{14}, R^{15}, and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

R^{15a} and R^{16a} are independently any of the R^{15} or R^{16} groups except hydroxy, nitro, amino or thio;

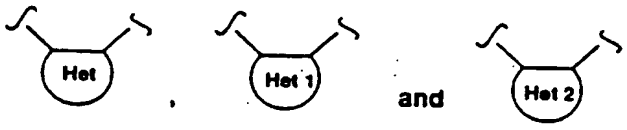
R^2, R^3, R^4 are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl,

alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

R^5 is alkyl , alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloheteroalkyl, heteroaryloxy, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloalkenyl-alkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all of the R^5 substituents and R^6 substituents (set out hereinafter) being optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroaryl-alkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino (wherein the amino includes 1 or 2 substituents which are alkyl, aryl or heteroaryl, or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylamino-carbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylamino-carbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkyl-carbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroaryl-

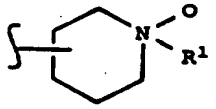
sulfonyl, or alkylsulfinyl. Where R^5 is phenyl, aryl, heteroaryl or cycloalkyl; this group preferably includes an ortho hydrophobic substituent such as alkyl, haloalkyl (with up to 5 halo groups), alkoxy, haloalkoxy (with up to 5 halo groups), aryl, aryloxy or arylalkyl;

R^6 is hydrogen or C_1-C_4 alkyl or C_1-C_4 alkenyl;



are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

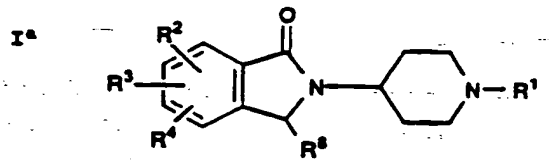
including N-oxides of the formulae I, Ii, II and IIi compounds, that is

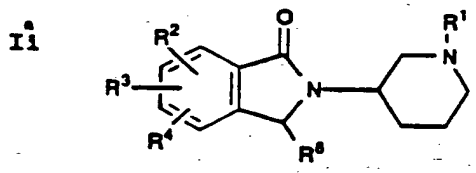


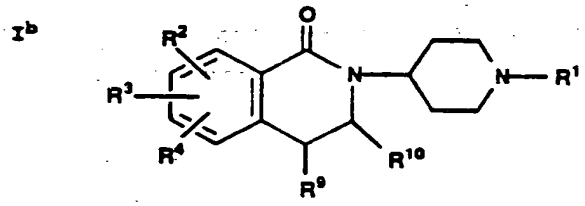
; and

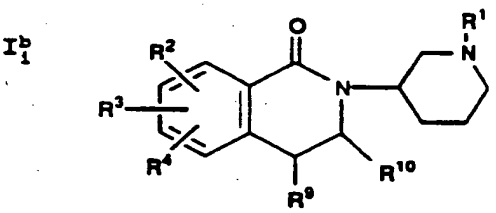
including pharmaceutically acceptable salts thereof such as alkali metal salts such as lithium sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butyl-amine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as chloride, bromide, iodide, tartrate, acetate, methanesulfonate, maleate, succinate, glutarate, and salts of naturally occurring amino acids such as arginine, lysine, alanine and the like, and prodrug esters thereof.

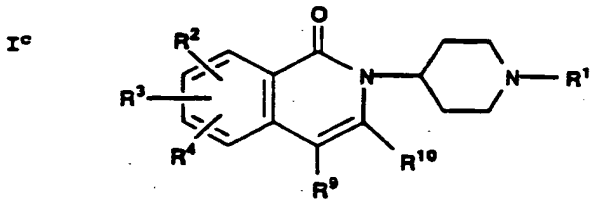
Thus, the compounds of formulae I and II of the invention encompass compounds of the structure

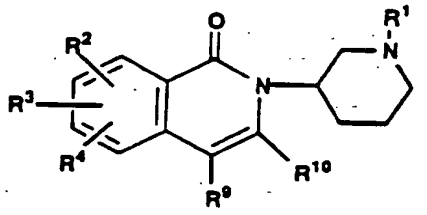


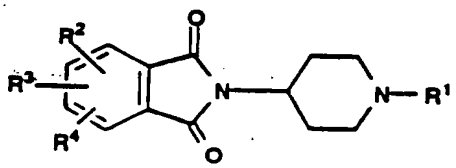


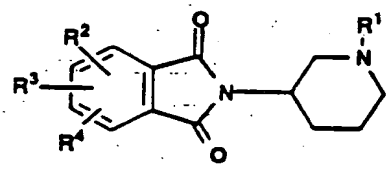


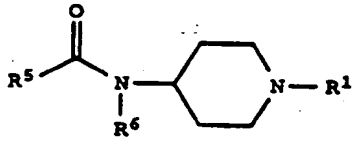


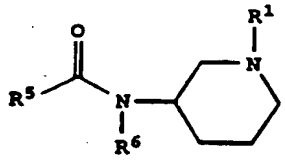


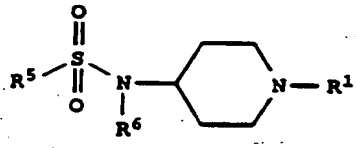
I_1^c 

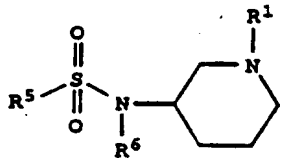
I^d 

I_1^d 

II^a 

II_1^a 

II^b 

II_1^b 

In addition, in accordance with the present invention, a method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity is provided, wherein a compound of formula I, Ii, II, or IIi as defined hereinbefore, is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

Furthermore, in accordance with the present invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a compound of formula I, Ii, II, or IIi as defined hereinbefore, is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

The following definitions apply to the terms as used throughout this specification, unless otherwise limited in specific instances.

The term "MTP" refers to a polypeptide or protein complex that (1) if obtained from an organism (e. g., cows, humans, etc.), can be isolated from the microsomal fraction of homogenized tissue; and (2) stimulates the transport of triglycerides, cholesterol esters, or phospholipids from synthetic phospholipid vesicles, membranes or lipoproteins to synthetic vesicles, membranes, or lipoproteins and which is distinct from the cholesterol ester transfer protein [Drayna et al., Nature 327, 632-634 (1987)] which may have similar catalytic properties. However, the MTP molecules of the present invention do not necessarily need to be catalytically active.

For example, catalytically inactive MTP or fragments thereof may be useful in raising antibodies to the protein.

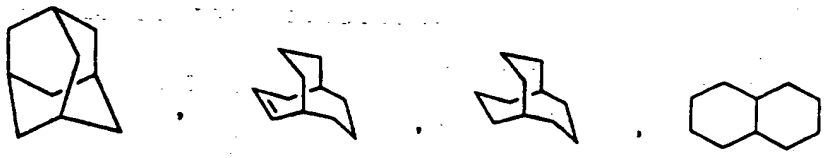
The phrase "stabilizing" atherosclerosis as used in the present application refers to slowing down the development of and/or inhibiting the formation of new atherosclerotic lesions.

The phrase "causing the regression of" atherosclerosis as used in the present application refers to reducing and/or eliminating atherosclerotic lesions.

Unless otherwise indicated, the term "lower alkyl", "alkyl" or "alk" as employed herein alone or as part of another group includes both straight and branched chain hydrocarbons, containing 1 to 40 carbons, preferably 1 to 20 carbons, more preferably 1 to 12 carbons, in the normal chain, such as methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethyl-pentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, and the like as well as such groups including 1 to 4 substituents such as halo, for example F, Br, Cl or I or CF_3, alkoxy, aryl, aryloxy, aryl(aryl) or diaryl, arylalkyl, arylalkyloxy, alkenyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkyloxy, amino, hydroxy, acyl, heteroaryl, heteroaryloxy, hetero-arylalkyl, heteroarylalkoxy, aryloxyalkyl, aryloxyaryl, alkylamido, alkanoylamino, arylcarbonylamino, nitro, cyano, thiol, haloalkyl, trihaloalkyl and/or alkylthio, as well as any of the other substituents as defined for R^5 and R^6.

Unless otherwise indicated, the term "cycloalkyl" as employed herein alone or as part of

another group includes saturated or partially unsaturated (containing 1 or 2 double bonds) cyclic hydrocarbon groups containing 1 to 3 rings, including monocyclicalkyl, bicyclicalkyl and tricyclicalkyl, containing a total of 3 to 20 carbons forming the rings, preferably 4 to 12 carbons, forming the ring and which may be fused to I or 2 aromatic rings as described for aryl, which include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl and cyclododecyl, cyclohexenyl,



any of which groups may be optionally substituted with 1 to 4 substituents such as halogen, alkyl, alkoxy, hydroxy, aryl, aryloxy, arylalkyl, cycloalkyl, alkylamido, alkanoylamino, oxo, acyl, arylcarbonylamino, amino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^5 or R^6.

The term "cycloalkenyl" as employed herein alone or as part of another group refers to cyclic hydrocarbons containing 5 to 20 carbons, preferably 6 to 12 carbons and 1 or 2 double bonds. Exemplary cycloalkenyl groups include cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclohexadienyl, and cycloheptadienyl, which may be optionally substituted as defined for cycloalkyl.

The term "polycycloalkyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges, preferably 6 to 12 carbons

and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctanyl, adamantanyl, [2.2.1]-bicycloheptanyl, [2.2.2]-bicyclooctanyl and the like and may be optionally substituted as defined for cycloalkyl.

The term "polycycloalkenyl" as employed herein alone or as part of another group refers to a bridged multicyclic group containing 5 to 20 carbons and containing 0 to 3 bridges and containing 1 or 2 double bonds, preferably 6 to 12 carbons and 1 or 2 bridges. Exemplary polycycloalkyl groups include [3.3.0]-bicyclooctenyl, [2.2.1]-bicycloheptenyl, [2.2.2]-bicyclooctenyl and the like and may be optionally substituted as defined for cycloalkyl.

The term "aryl" or "Ar" as employed herein alone or as part of another group refers to monocyclic and bicyclic aromatic groups containing 6 to 10 carbons in the ring portion (such as phenyl or naphthyl) and may optionally include one to three additional rings fused to Ar (such as aryl, cycloalkyl, heteroaryl or cycloheteroalkyl rings) and may be optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, haloalkyl, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, trifluoromethyl, trifluoromethoxy, alkynyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, aryloxy, aryloxyalkyl, arylalkoxy, arylthio, arylazo, heteroarylalkyl, heteroarylalkenyl, heteroarylheteroaryl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino wherein the amino includes 1 or 2 substituents (which are alkyl, aryl or any of the other aryl compounds mentioned in the definitions), thiol, alkylthio,

arylthio, heteroarylthio, arylthioalkyl, alkoxyarylthio, alkylcarbonyl, arylcarbonyl, alkylaminocarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonylamino or arylsulfonaminocarbonyl, or any of the substituents as defined for the R^5 or R^6 groups set out above.

The term "aralkyl", "aryl-alkyl" or "aryllower alkyl" as used herein alone or as part of another group refers to alkyl groups as discussed above having an aryl substituent, such as benzyl or phenethyl, or naphthylpropyl, or an aryl as defined above.

The term "lower alkoxy", "alkoxy", "aryloxy" or "aralkoxy" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to an oxygen atom.

The term "amino" as employed herein alone or as part of another group may optionally be substituted with one or two substituents such as alkyl and/or aryl.

The term "lower alkylthio", alkylthio", "arylthio" or "aralkylthio" as employed herein alone or as part of another group includes any of the above alkyl, aralkyl or aryl groups linked to a sulfur atom.

The term "lower alkylamino", "alkylamino", "arylamino", or "arylalkylamino" as employed herein alone or as part of another group includes any of the above alkyl, aryl or arylalkyl groups linked to a nitrogen atom.

The term "acyl" as employed herein by itself or part of another group as defined herein, refers to an organic radical linked to a carbonyl ($\overset{O}{\overset{\|}{C}}$) group, examples of acyl groups include alkanoyl, alkenoyl, aroyl, aralkanoyl, heteroaroyl, cycloalkanoyl and the like.

The term "alkanoyl" as used herein alone or as part of another group refers to alkyl linked to a carbonyl group.

Unless otherwise indicated, the term "lower alkenyl" or "alkenyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 3 to 12 carbons, and more preferably 1 to 8 carbons in the normal chain, which include one to six double bonds in the normal chain, such as vinyl, 2-propenyl, 3-butenyl, 2-butenyl, 4-pentenyl, 3-pentenyl, 2-hexenyl, 3-hexenyl, 2-heptenyl, 3-heptenyl, 4-heptenyl, 3-octenyl, 3-nonenyl, 4-decenyl, 3-undecenyl, 4-dodecenyl, 4,8,12-tetradecatrienyl, and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cyclo-alkyl, amino, hydroxy, heteroaryl, cyclohetero-alkyl, alkanoylamino, alkylamido, arylcarbonylamino, nitro, cyano, thiol and/or alkylthio, as well as any of the other substituents as defined for R^5 or R^6.

Unless otherwise indicated, the term "lower alkynyl" or "alkynyl" as used herein by itself or as part of another group refers to straight or branched chain radicals of 2 to 20 carbons, preferably 2 to 12 carbons and more preferably 2 to 8 carbons in the normal chain, which include one triple bond in the normal chain, such as 2-propynyl, 3-butynyl, 2-

butynyl, 4-pentynyl, 3-pentynyl, 2-hexynyl, 3-hexynyl, 2-heptynyl, 3-heptynyl, 4-heptynyl, 3-octynyl, 3-nonynyl, 4-decynyl,3-undecynyl, 4-dodecynyl and the like, and which may be optionally substituted with 1 to 4 substituents, namely, halogen, haloalkyl, alkyl, alkoxy, alkenyl, alkynyl, aryl, arylalkyl, cycloalkyl, amino, heteroaryl, cycloheteroalkyl, hydroxy, alkanoylamino, alkylamido, arylcarbonyl-amino, nitro, cyano, thiol, and/or alkylthio, as well as any of the other substituents as defined for R^5 or R^6.

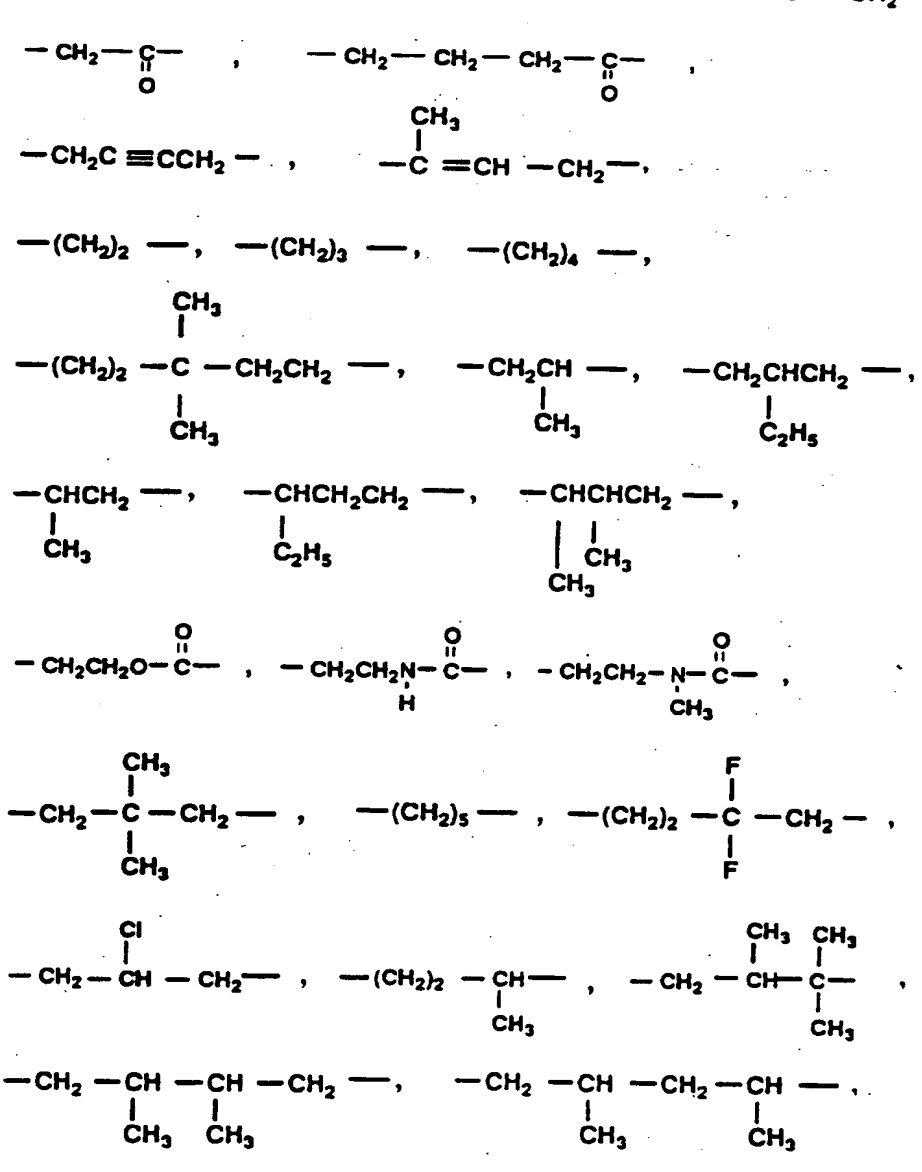
The term "alkylene" as employed herein alone or as part of another group (which also encompasses "alkyl" as part of another group such as arylalkyl or heteroarylalkyl) refers to alkyl groups as defined above having single bonds for attachment to other groups at two different carbon atoms and may optionally be substituted as defined above for "alkyl". The definition of alkylene applies to an alkyl group which links one function to another, such as an arylalkyl substituent.

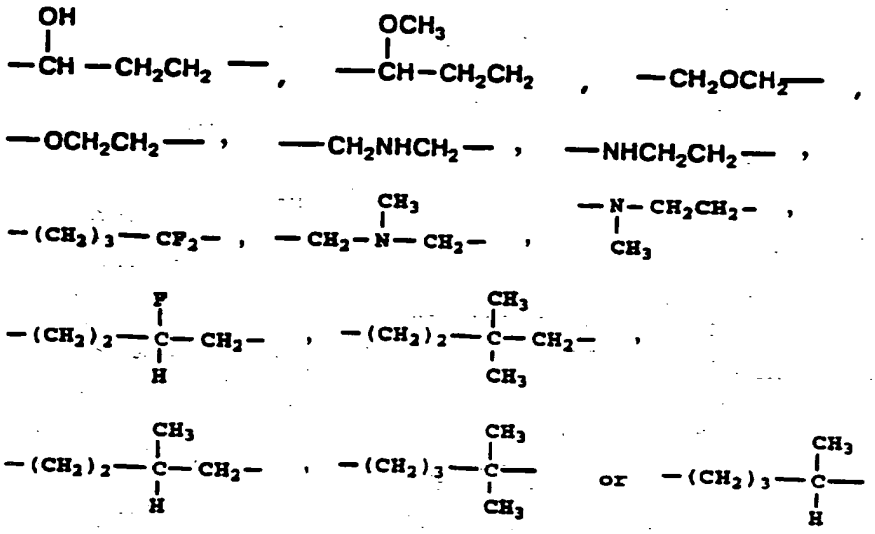
Ther terms "alkenylene" and "alkynylene" as employed herein alone or as part of another group (which also encompass "alkenyl" or "alkynyl" as part of another group such as arylalkenyl or arylalkynyl), refer to alkenyl groups as defined above and alkynyl groups as defined above, respectively, having single bonds for attachment at two different carbon atoms.

Suitable alkylene, alkenylene or alkynylene groups or $(CH_2)_n$ or $(CH_2)_p$ (which may include alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1,2, or 3 alkyl, alkoxy, aryl, heteroaryl, cycloheteroalkyl, alkenyl, alkynyl, oxo, aryloxy, hydroxy, halogen substituents

as well as any of the substituents defined for R^5 or R^6, and in addition, may have one of the carbon atoms in the chain replaced with an oxygen atom, N-H, N-alkyl or N-aryl.

Examples of alkylene, alkenylene, alkynylene, $(CH_2)_n$ and $(CH_2)_p$ groups include

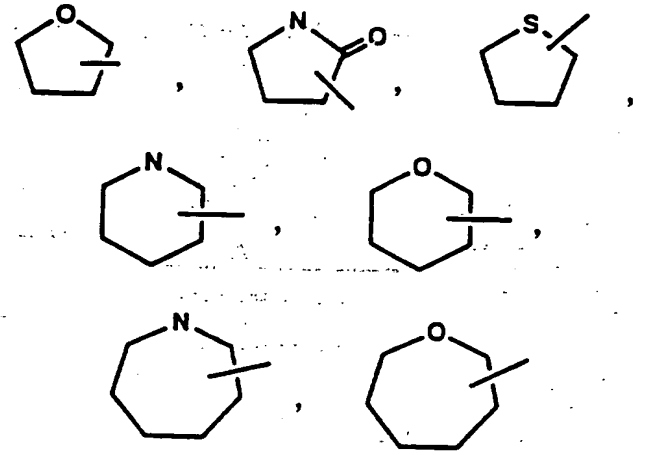




The term "halogen" or "halo" as used herein alone or as part of another group refers to chlorine, bromine, fluorine, and iodine as well as CF_3, with chlorine or fluorine being preferred.

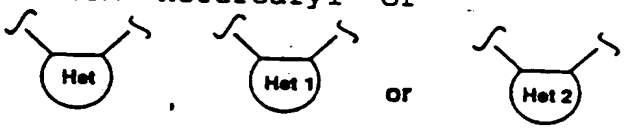
The term "metal ion" refers to alkali metal ions such as sodium, potassium or lithium and alkaline earth metal ions such as magnesium and calcium, as well as zinc and aluminum.

The term "cycloheteroalkyl" as used herein alone or as part of another group refers to a 5-, 6- or 7-membered saturated or partially unsaturated ring which includes 1 to 2 hetero atoms such as nitrogen, oxygen and/or sulfur, linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as

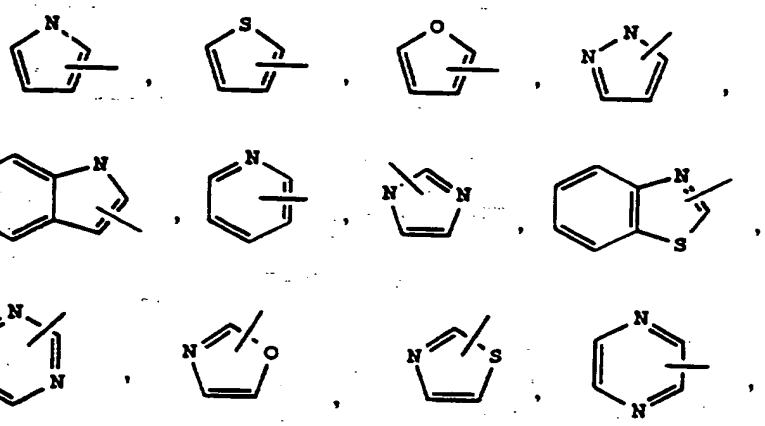


and the like. The above groups may include 1 to 3 substituents such as any of the R^1, R^5 or R^6 groups as defined above. In addition, any of the above rings can be fused to 1 or 2 cycloalkyl, aryl, heteroaryl or cycloheteroalkyl rings.

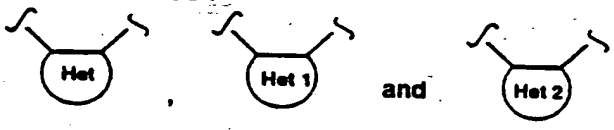
The term "heteroaryl" or



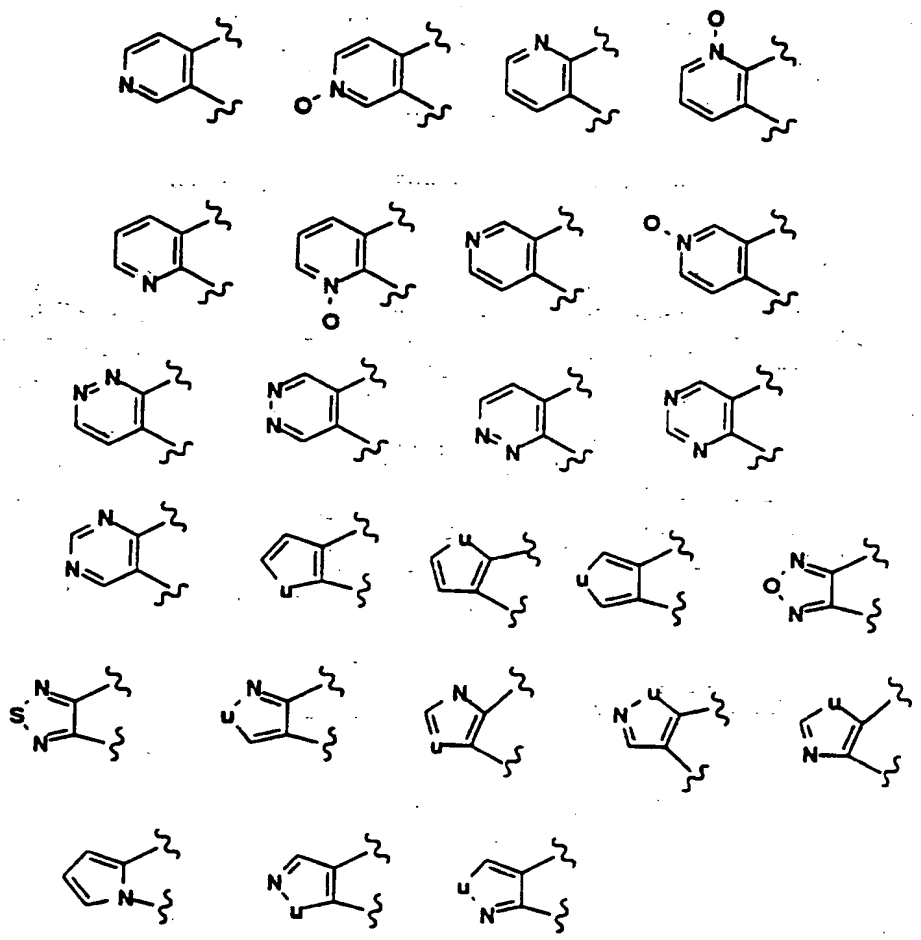
(also referred to as heteroaryl) as used herein alone or as part of another group refers to a 5- or 6-membered aromatic ring which includes 1, 2, 3 or 4 hetero atoms such as nitrogen, oxygen or sulfur, and such rings fused to an aryl, cycloalkyl, heteroaryl or cycloheteroalkyl ring (e.g. benzothiophenyl, indolyl), linked through a carbon atom or a heteroatom, where possible, optionally via the linker $(CH_2)_p$ (which is defined above), such as



and the like, and includes all possible N-oxide derivatives.



are the same or different as defined hereinbefore and are attached to the central ring of the indenyl or fluorenyl type group at adjacent positions (that is ortho or 1,2-positions). Examples of such groups include



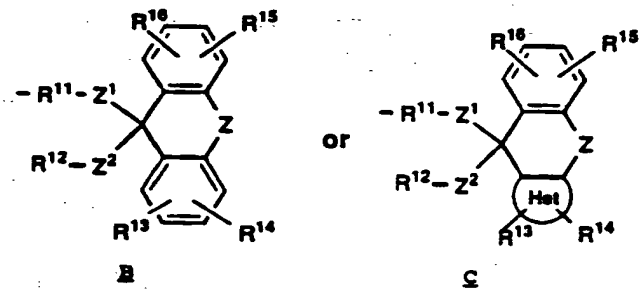
wherein u is selected from O, S, and NR^{7a};
R^{7a} is H, lower alkyl, aryl, $-C(O)R^{7b}$, $-C(O)OR^{7b}$;
R^{7b} is alkyl or aryl, and includes all possible N-oxide derivatives.

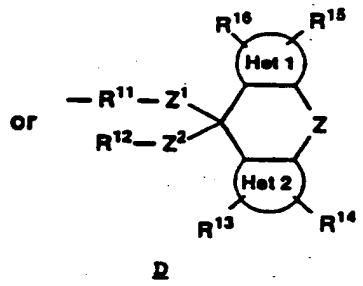
The heteroaryl groups including the above groups may optionally include 1 to 4 substituents such as any of the substituents listed for aryl, or those substituents indicated for R^5 or R^6 groups as defined above. In addition, any of the above rings can be fused to a cycloalkyl, aryl, heteroaryl or cycloheteroalkyl ring.

The term cycloheteroalkylalkyl" as used herein alone or as part of another group refers to cycloheteroalkyl groups as defined above linked through a C atom or heteroatom to a $(CH_2)_p$ chain.

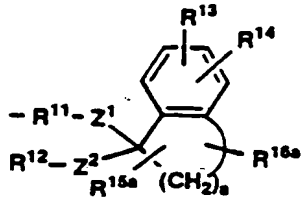
The term "heteroarylalkyl" or "heteroarylalkenyl" as used herein alone or as part of another group refers to a heteroaryl group as defined above linked through a C atom or heteroatom to a $-(CH_2)_p-$ chain, alkylene or alkenylene as defined above.

The term "fluorenyl" or "fluorenyl analog" or "fluorenyl-type group" as employed herein refers to a group of the structure:





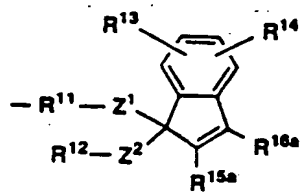
The term "indenyl-type group" as emplyed herein refers to a group of the structure



E

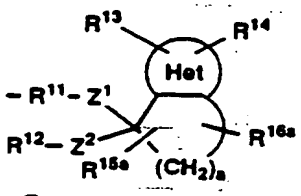
(a = 2,3 or 4)

or



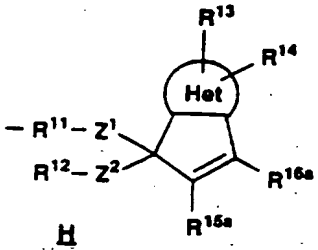
E

or



G

or



H

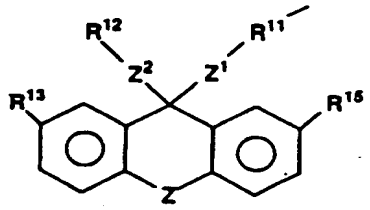
;

Z, Z^1, Z^2, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}, R^{15a} and R^{16a} as used in the above groups A through H are as defined hereinbefore.

Preferred are compounds of formulae I and II wherein

R^1 is

or



B'

(including where Z^1 is a bond and R^{11} is alkylene or alkenylene and Z^2 is  ,  ,  or  , and R^{12} is C_1-C_3 alkyl or 1,1,1-trifluoroethyl, R^{13} is H or F and R^{15} is H or F, and Z is a bond or O; and where R^{11} is alkylene or alkenylene or alkylene

substituted with oxo, R^{12} is alkyl, alkenyl, aralkyl, aralkenyl, Z is O, S or a bond).

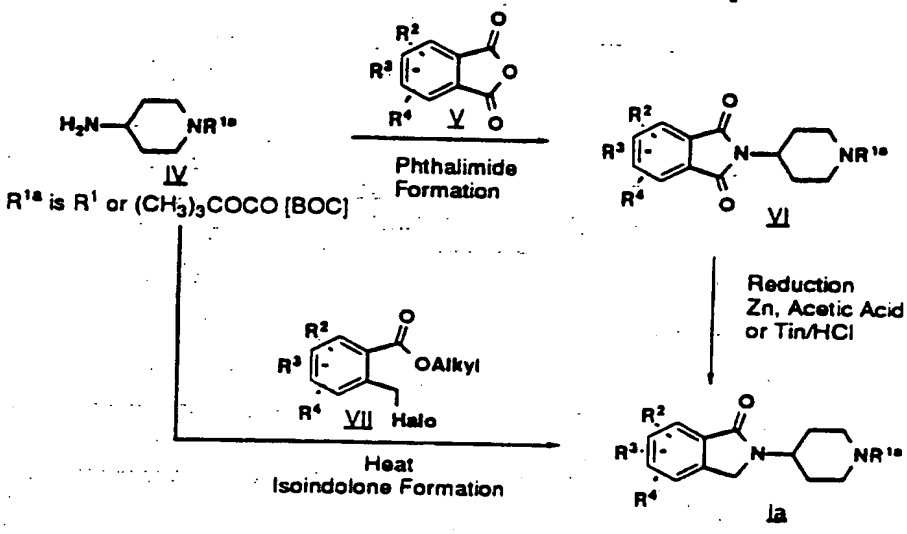
In structure I, it is preferred that R^2, R^3 and R^4 are each H and X is CH_2, CH_2CH_2, or CH=CH.

In structure II, it is preferred that R^6 is H or CH_3 and R^5 is cycloalkyl, phenyl, aryl or heteroaryl, or cycloalkyl, phenyl, aryl heteroaryl having an ortho hydrophobic substituent which is alkyl, alkoxy, haloalkyl (containing up to five halo groups), trifluoromethyl, aryl, aryloxy, arylalkyl, arylalkoxy, haloalkoxy (containing up to five halo groups).

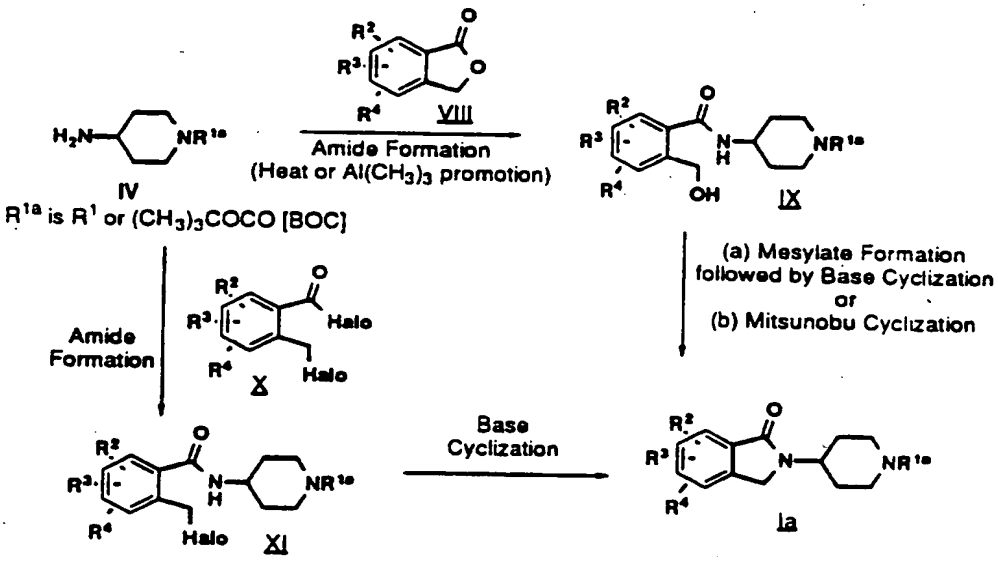
It is to be understood that combinations of substituents which lead to chemically unstable molecules are not included within the scope of the present invention; for example, compounds of the invention will not include -O-O-, -O-C-OH, N-C-OH and -S-C-OH linkages.

The compounds of formulae I, Ii, II, and IIi may be prepared by the exemplary processes described in the following reaction schemes. Exemplary reagents and procedures for these reactions appear hereinafter and in the working Examples.

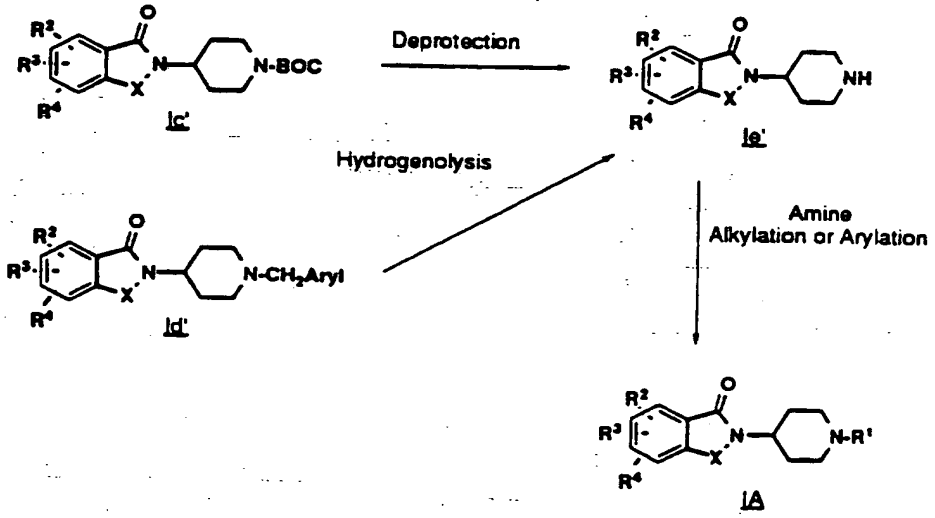
Scheme I. Routes to Isoindolinone Piperidines I



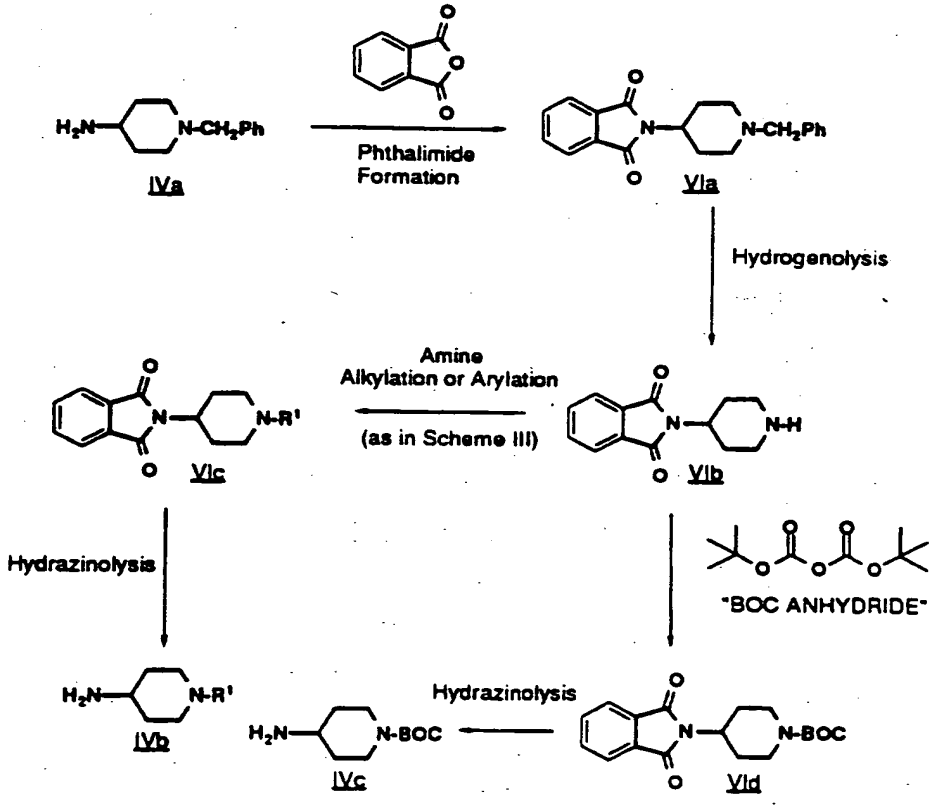
Scheme II. Additional Routes to Isoindolinone Piperidines I



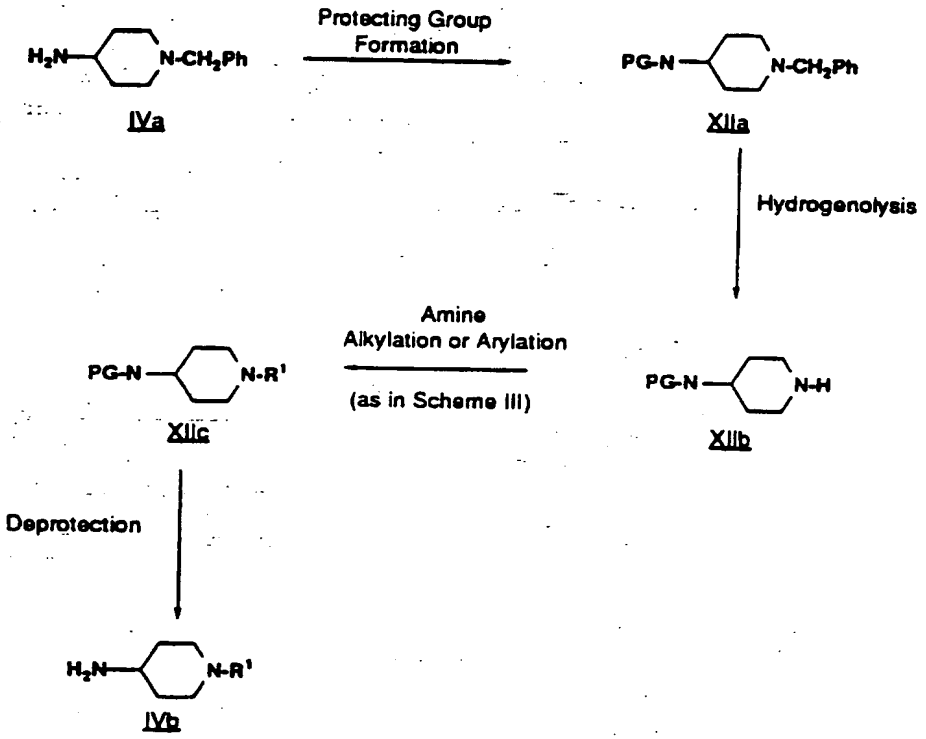
Scheme III. Introduction of R^1 by Alkylation or Arylation



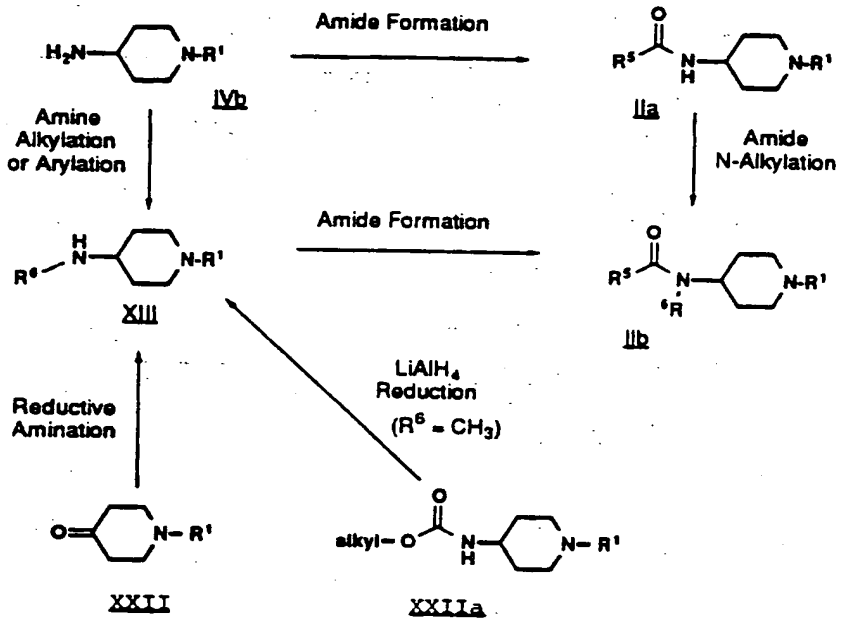
Scheme IV. Routes to Starting Materials IVb and IVc



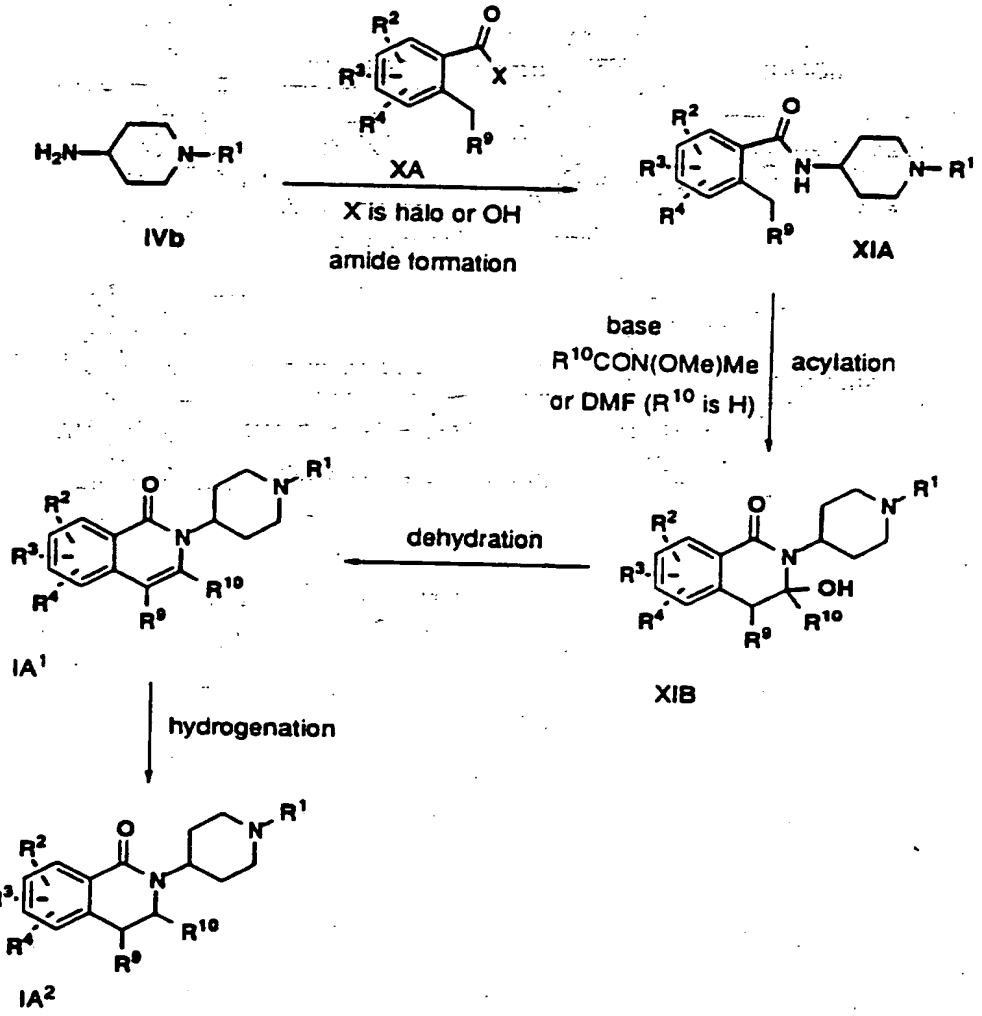
Scheme V. General Routes to Starting Materials IVb



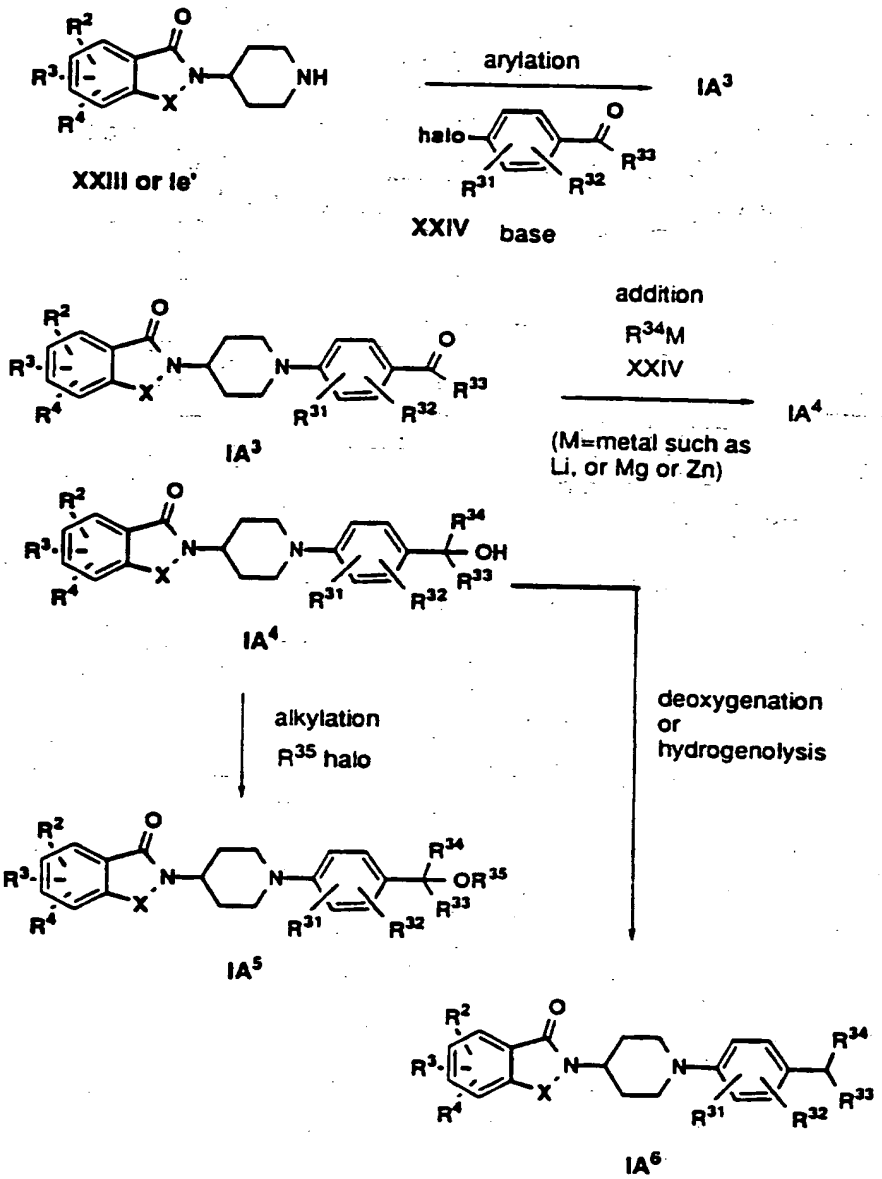
Schemes VI and VII. General Routes to II



Scheme VIII Preparation of Compounds IA^1, IA^2



Scheme IX Preparation of Compounds IA^3-IA^6



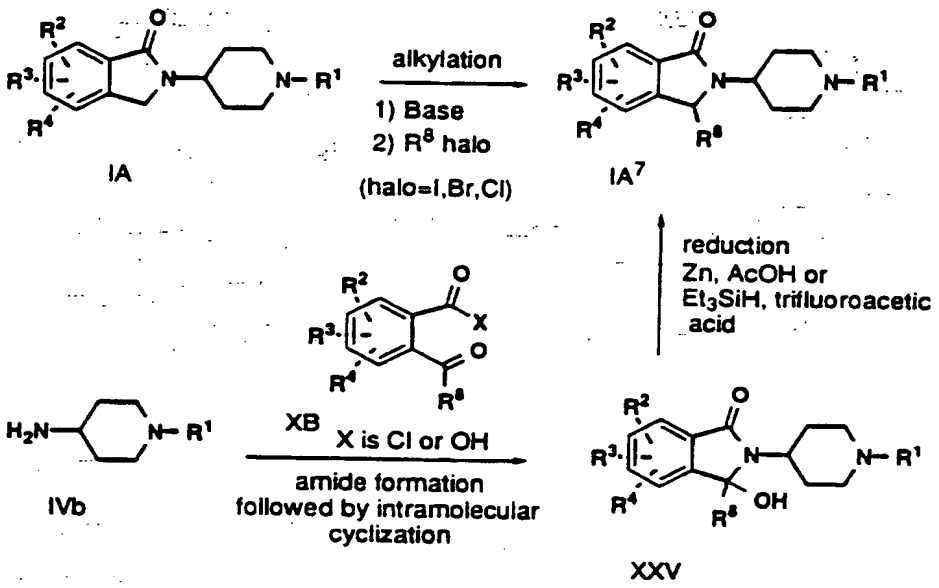
R^{31} and R^{32} are independently selected from any of the R^2, R^3, or R^4 radicals;

R^{33} and R^{34} are independently selected from any of the R^1 radicals as well as aryloxy, alkoxy,

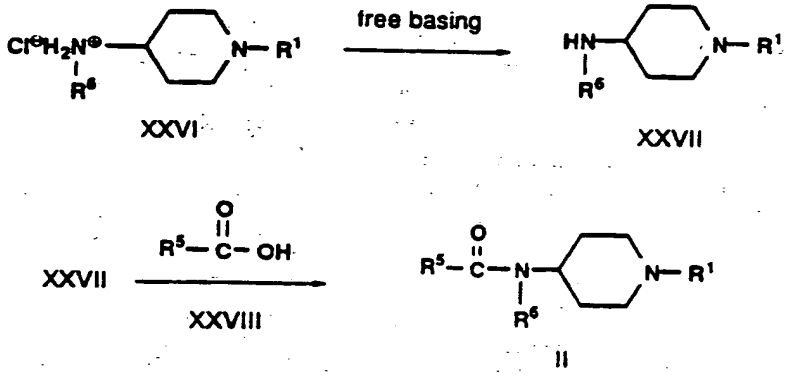
arylalkoxy, heteroarylalkoxy and heteroaryloxy, at least one of R^{33} and R^{34} being an R^1 radical;

R^{35} can be any of the R^1 radicals.

Schemes X and XI Preparation of Compound IA^7



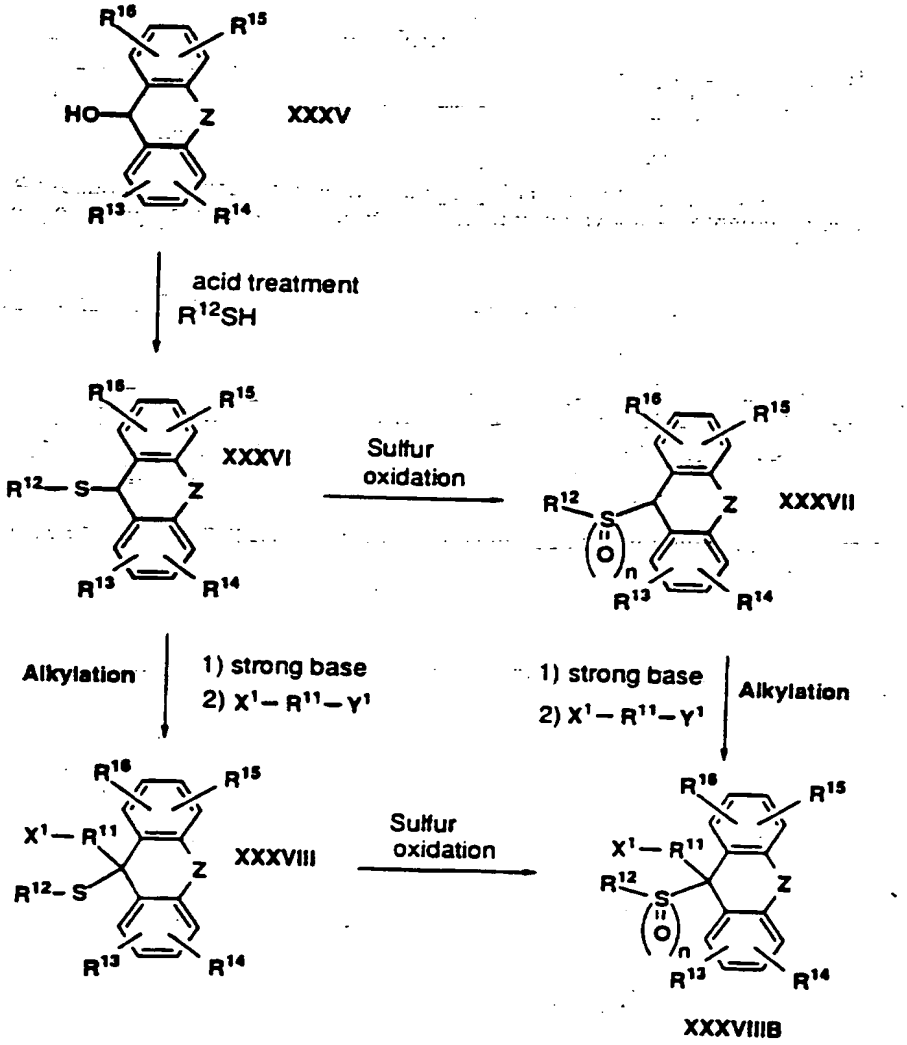
Scheme XII Preparation of Compound II
(Robotic Amide Coupling)



In the following Schemes XII et al, in the fluorenyl rings or fluorenyl analogs, the fused aryl groups:

may each optionally be replaced by a 5- or 6-membered heteroaryl ring as defined herein.

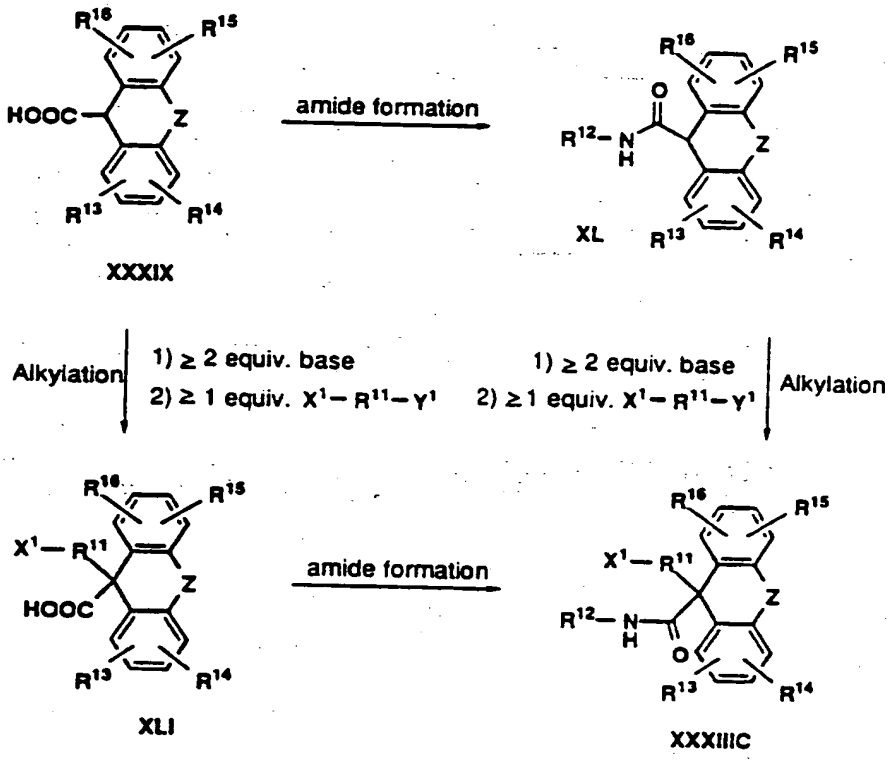
Scheme XIII - Preparation of Intermediates where Z^2 is S, SO or SO_2



X^1, Y^1 are same or different halo or Osulfonate

n = 1 or 2

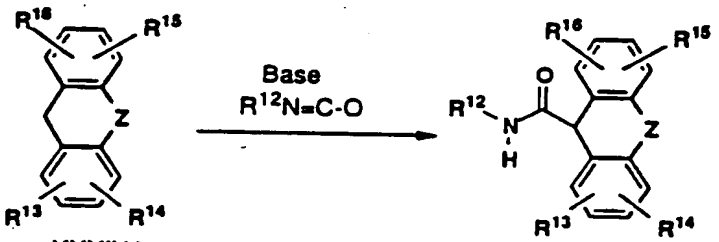
Scheme XIV - Preparation of A (Intermediates where Z^2 is NHCO)



X^1, Y^1 are same or different halo or Osulfonate

Scheme XIVA

Alternative Procedure for Preparing Intermediate XL
(Shown in Scheme XIV)

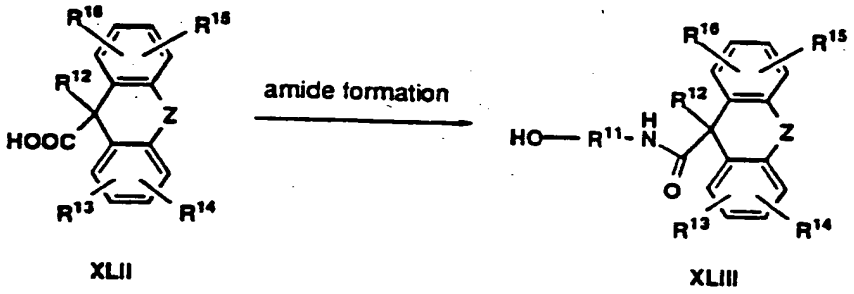


XXXIXA XL

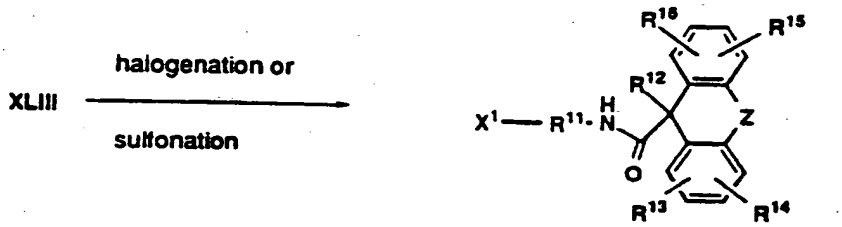
In carrying out the above reaction, bases such as n-butyllithiun, lithium bis(trimethylsilyl) amide and sodium bis(trimethylsilyl) amide may be employed in an aprotic solvent such as THF, at between -78°C and 35°C.

It is preferable to have the starting material and isocyanate ($R^{12}N=C-O$) together in solvent, and then add the base, and optionally add further excess isocyanate subsequently.

Scheme XV - Preparation of Intermediate where Z^1 is $-\overset{H}{N}-\overset{O}{\overset{\|}{C}}-$



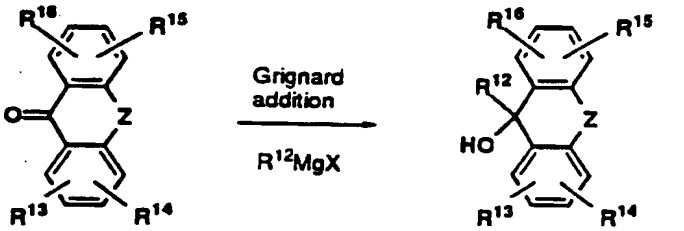
XLII XLIII



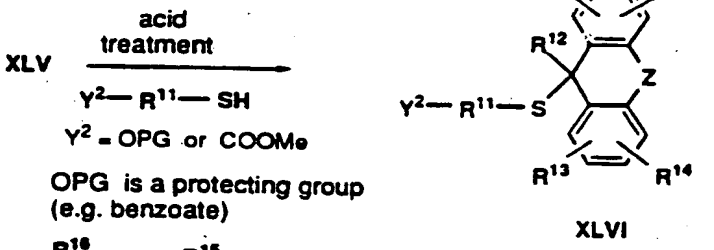
XXXIIID

X^1 is halo or Osulfonate

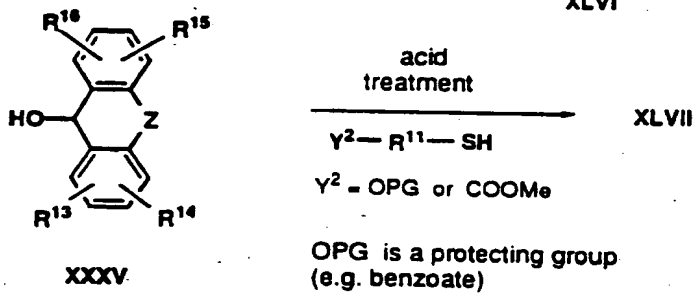
Scheme XVI



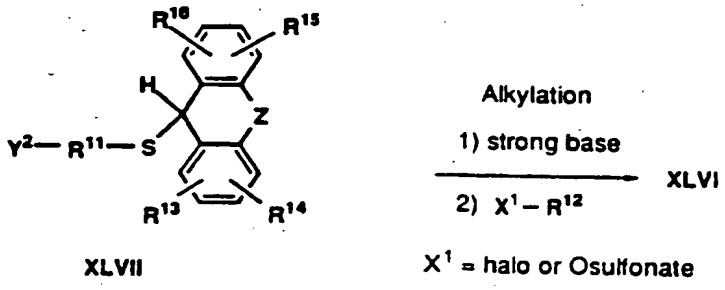
XLIV XLV



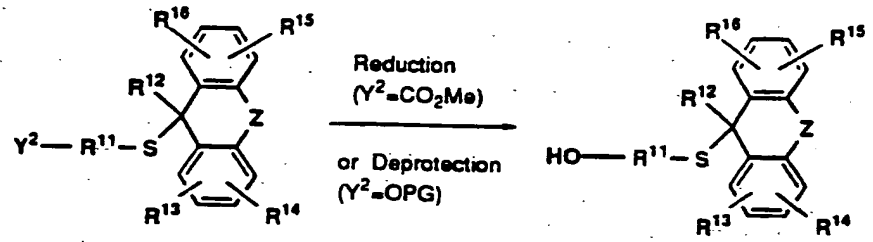
XLVI



XXXV

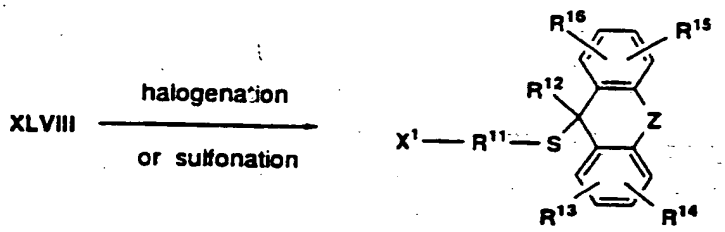


XLVII



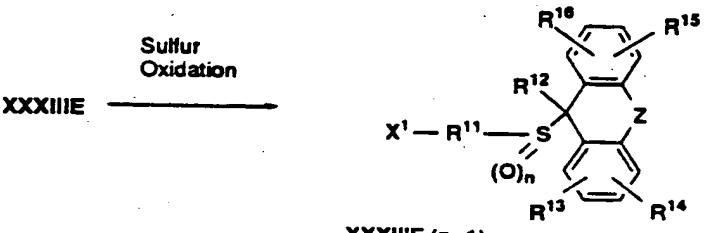
XLVI

XLVIII



X¹ is halo or Osulfonate

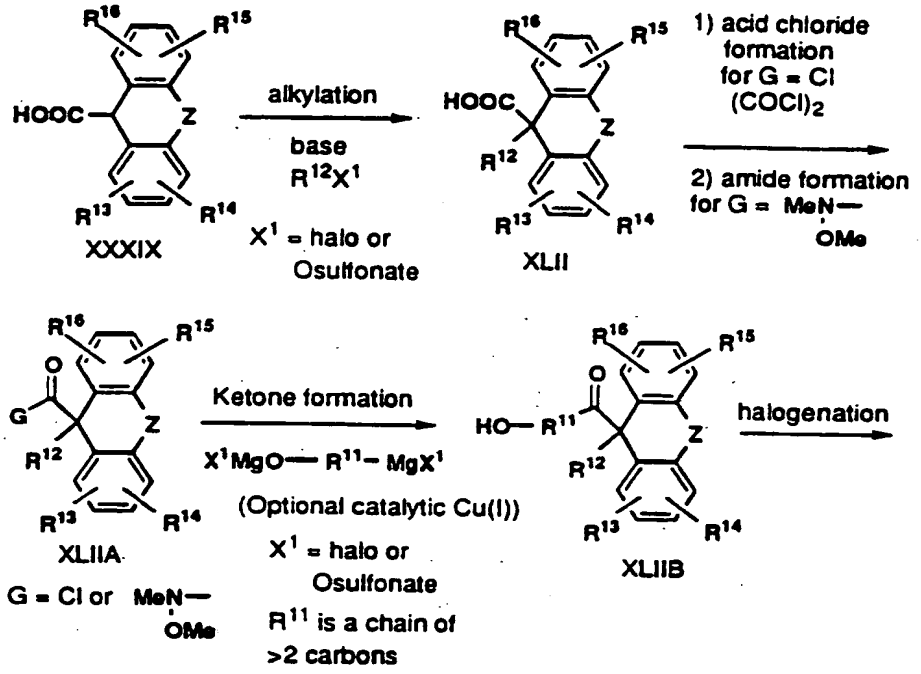
XXXIIIE



XXXIIIF (n=1)

XXXIIIG (n=2)

Scheme XVIA Preparation of Ketones



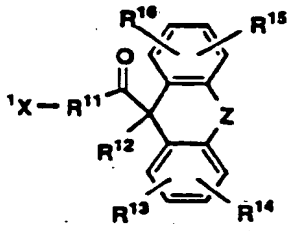
XXXIX

XLII

XLIIA

G = Cl or MeN(OMe)—

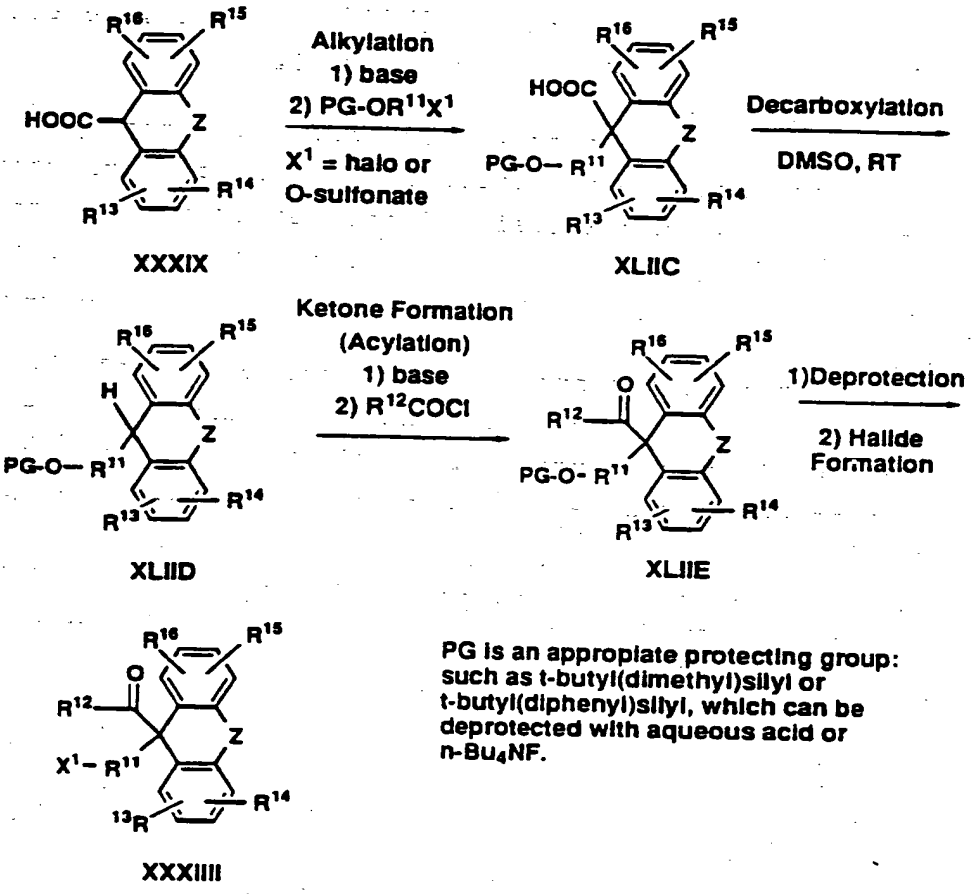
XLIIB



XXXIIIH

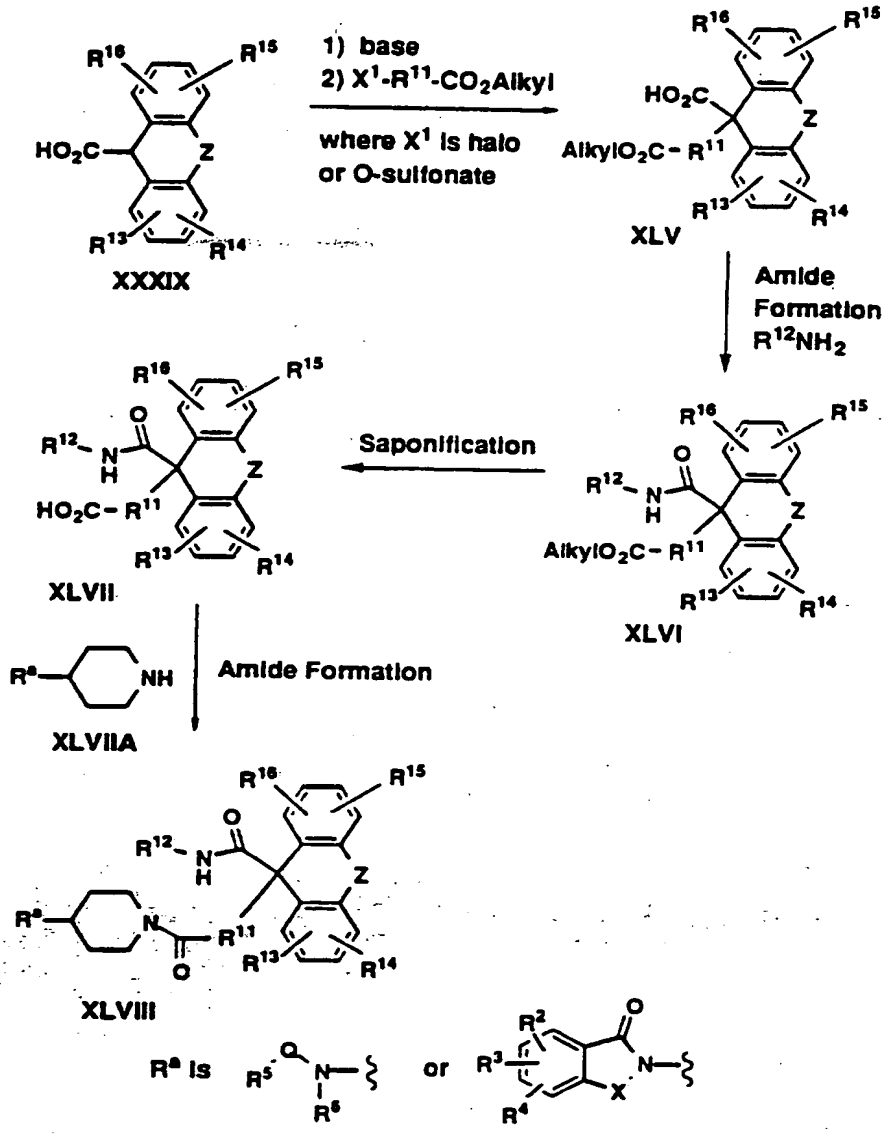
X^1 = halo or Osulfonate

Scheme XVIB. Preparation of Ketones (Preferred Route)

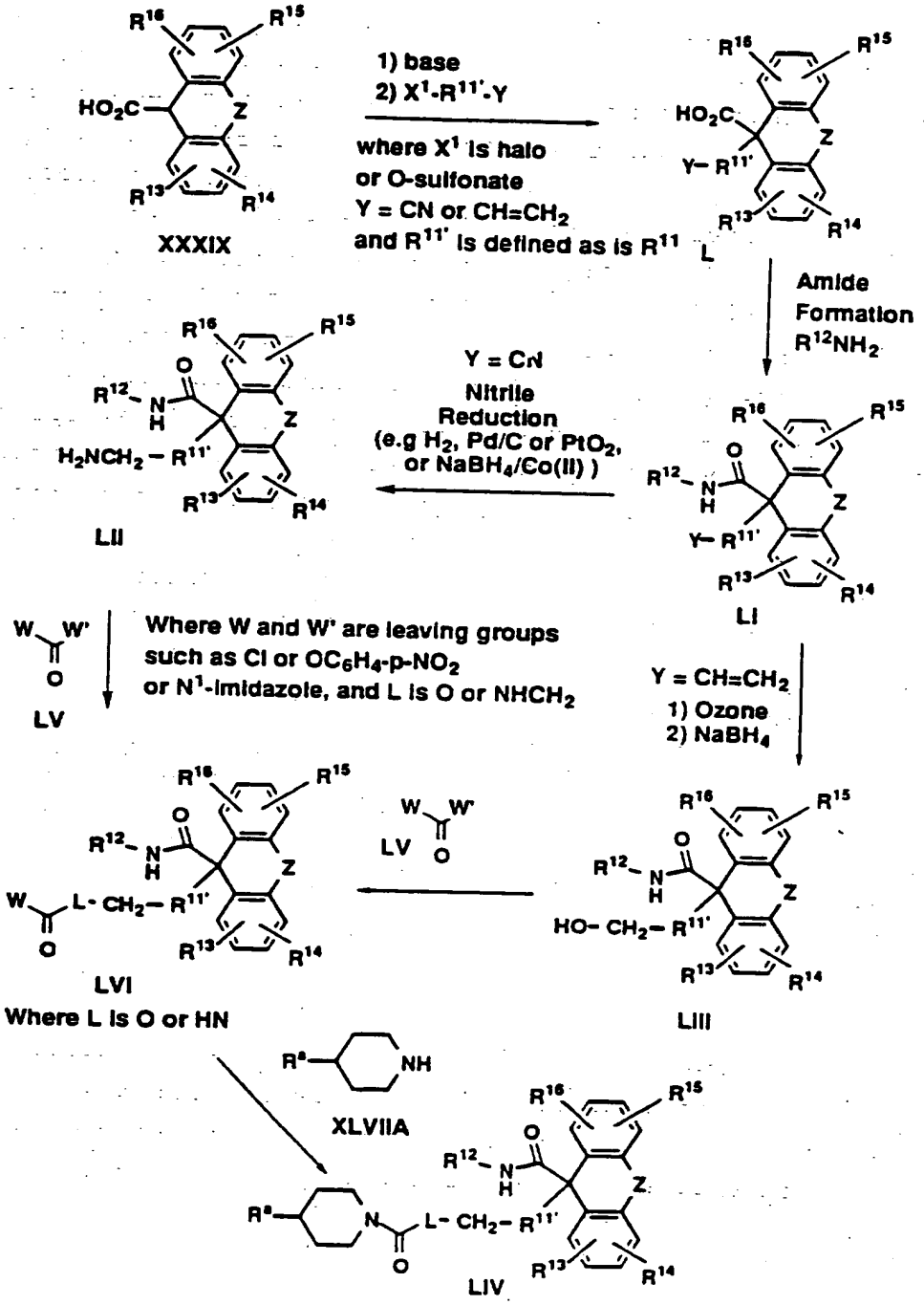


XXXIX XLIIC XLIID XLIIE XXXIIII

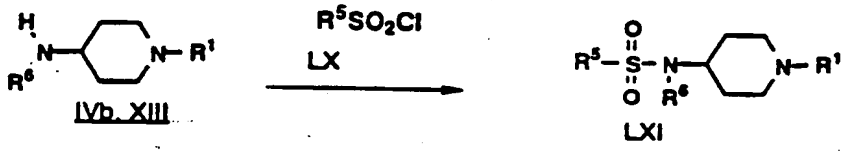
Scheme XVIIA - Preparation of Amide Linked Compounds



Scheme XVIIB - Preparation of Carbamate and Urea Linked Compounds



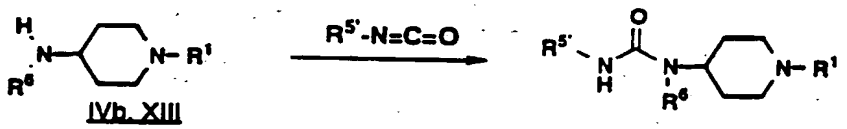
Scheme XVIIIA - Formation of Sulfonamides



IVb, XIII LXI

(Reaction in a variety of solvents (CH_2Cl_2, THF, pyridine) optionally in the presence of a tertiary amine base, such as pyridine or triethyl amine).

Scheme XVIIIB - Formation of Ureas (R^5 is Amino)

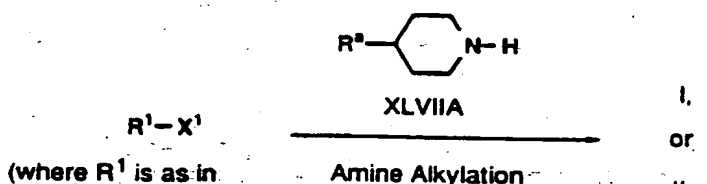


IVb, XIII LXII

(1 to 10 equiv of R-C=N=O, in aprotic solvent such as toluene, from 0°C to 150°C).

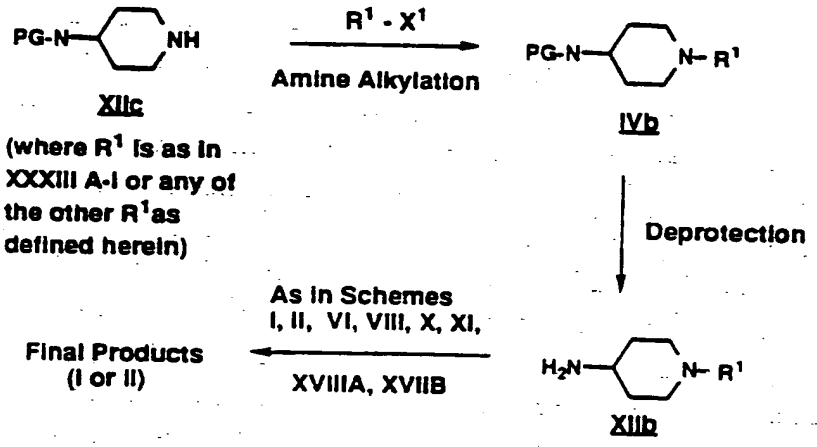
($R^{5'}$ is alkyl, aryl, heteroaryl or arylalkyl).

Scheme XIXA - General Route to Final Product



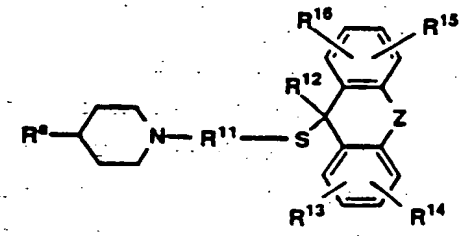
(where R^1 is as in XXXIII A-K or any other R^1 as defined herein)

Scheme XIXB General Route to Final Products (I or II)



(Example of a protected nitrogen (PG-N) is the t-BuOC=ONH (BOC amino) group, which can be deprotected under mild conditions, such as anhydrous HCl in dioxane or neat trifluoroacetic acid).

Scheme XX - Oxidation of sulfur at the end of the reaction sequence



I9

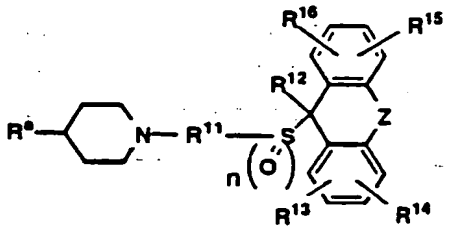
1) HCl* or CF_3CO_2H*

2) Selective sulfur oxidation

3) base

I10

*Acid pretreatment protects basic piperidine from oxidation

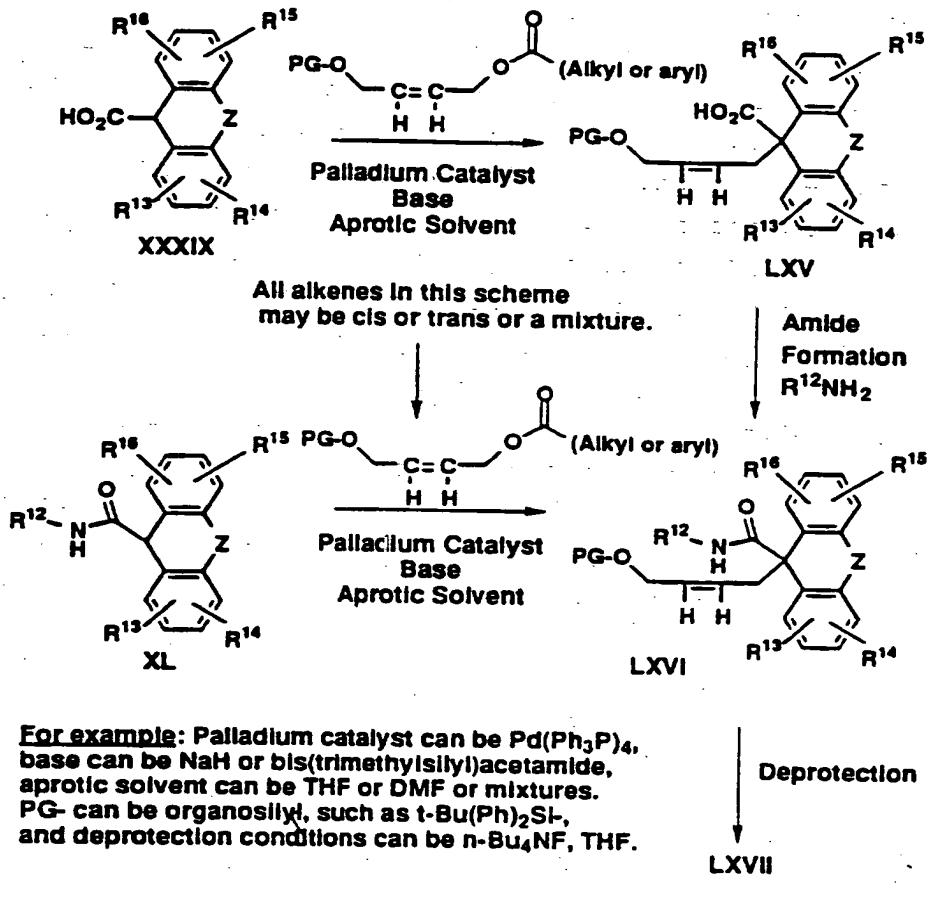


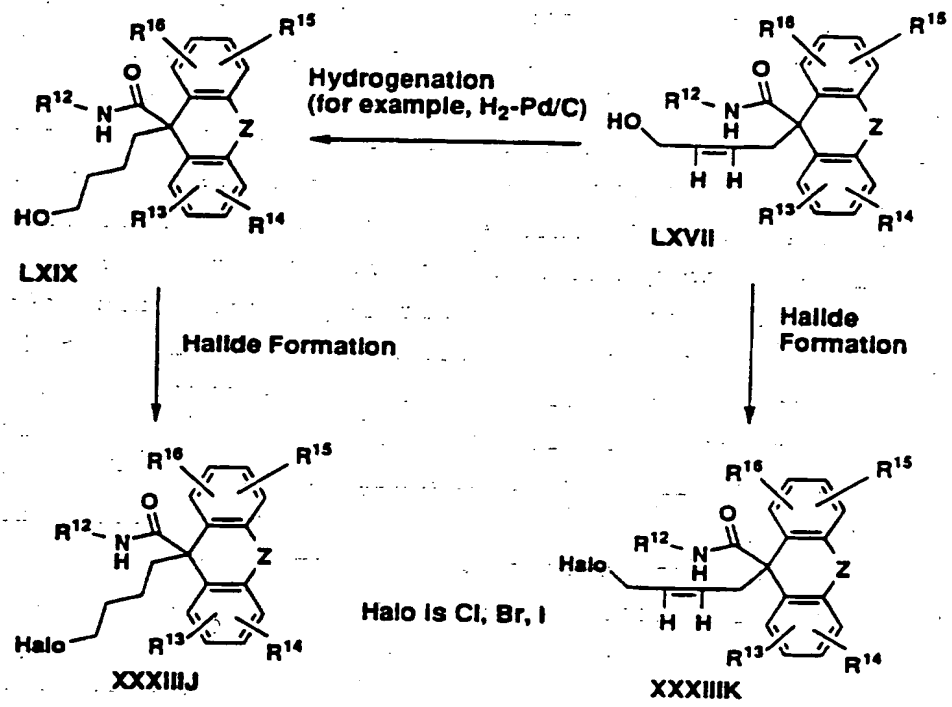
I10

n = 1 or 2

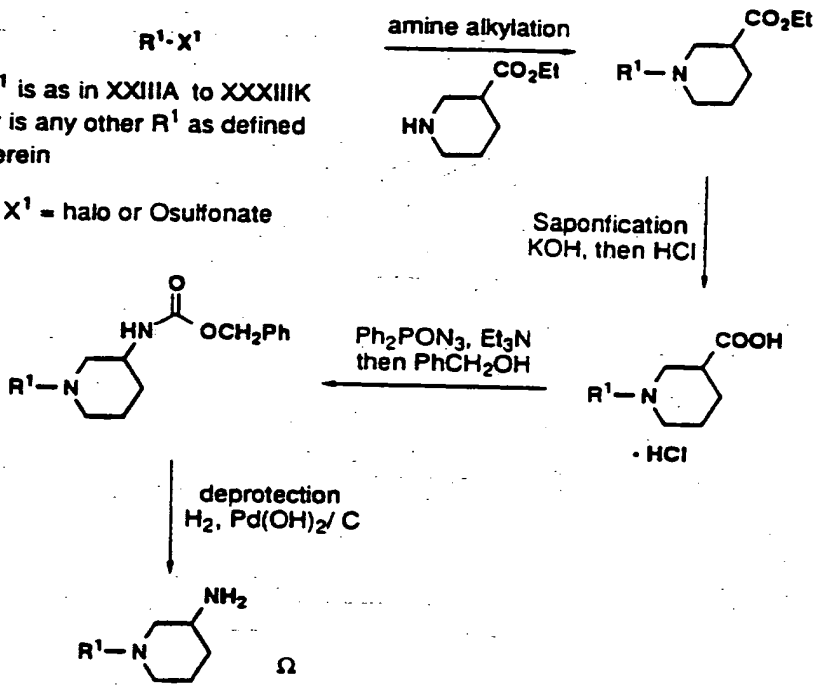
(R^a is defined as in Scheme XVIIA)

Scheme XXI - Preparation of Halide Intermediates



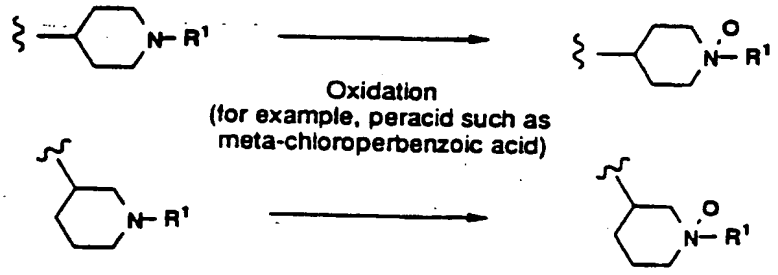

Hydrogenation
(for example, H_2-Pd/C)
LXIX
LXVII
Halide Formation
Halide Formation
Halo is Cl, Br, I
XXXIIIJ
XXXIIIK

Scheme XXII - Preparation of 3-Substituted Piperidine Starting Materials



Intermediate Ω can be utilized as a starting material to prepare 3-substituted isomers Ii and IIi via the same methodology as outlined in the Schemes herein, specifically Schemes I, II, IV, V, VI, VII, VIII, X, XI, XII, XVIIIA, XVIIIB, XIXB, XX, XXIII.

Scheme XXIII - Preparation of N-Oxides of Formulae I and II compounds



It is to be understood that in Schemes I to VI, VIII to XII, XVIIA, XVIIB, XVIIIA, XVIIIB, XIXA, XIXB, XX and XXI (which relate to preparation of compounds of the invention of formula I or II), the starting materials which are depicted as the 4-substituted piperidine isomers may be substituted with the corresponding 3-substituted piperidine isomers to afford the corresponding compounds of the invention Ii or IIi which include the 3-substituted piperidine isomer.

In the above Reaction Schemes XII through XXI, the starting fluorenyl-type acid XXVIII, alcohol XXXV, acids XXXIX and XLII, ketone XLIV, hydride XXXIXA, and amide XL groups may be substituted with corresponding acid, alcohol, ketone, hydride and amide containing fluorenyl type groups as set out in B, C and D or indenyl-type groups as set out in E, F, G and/or H to provide an intermediate compound for use in preparing a compound of formula I, I', II or II' of the invention as per Reaction Schemes I to XXIII.

Phthalimide formation (Reaction Schemes I, IV) may be carried out by heating to about 80 to 150°C in

an oil bath optionally in an inert solvent or by various other procedures known in the art.

Reduction (Reaction Scheme I) may be carried out by treatment with such reducing agents as zinc in the presence of acetic acid or tin in the presence of hydrochloric acid under an inert atmoshphere (e.g., argon).

Isoindolone formation (Reaction Scheme I) may be carried out by heating in the range of about 50 to 150°C in an organic solvent (e.g., toluene, ethanol, dimethylformamide) optionally in the presence of a salt (e.g., potassium carbonate) or a tertiary amine base (e.g., 2,6-di-t-butylpyridine or triethylamine).

Amide formation (Reaction Schemes II, VI, VII, VIII, X, XI, XII, XIV, XIVA, XV, XVI, XVI, XVIA, XVIIA, XVIIB), XXI may be carried out by a number of methods known in the art. For example, an amine substrate may be treated with (1) an acid halide $R^5C(O)$halo or compound X or XA in an aprotic solvent, optionally in the presence of a tertiary amine base (e.g., triethylamine); (2) the acid halide in the presence of an aqueous base under Schotten-Baumann conditions; (3) a free carboxylic acid (R^5CO_2H) in the presence of a coupling agent such as dicyclohexylcarbodiimide (DCC), diisopropyl carbodiimide (DIC) or 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (WSC), optionally in the presence of 1-hydroxybenzotriazole (HOBT); (4) the free acid in the presence of N, N-carbonyl-diimidazole in an aprotic organic solvent followed by the amine substrate; (5) trialkylaluminum (e.g., $Al(CH_3)_3$) in an aprotic solvent, followed by an ester (e.g., R^5CO_2alkyl or compound VIII) or (6) mixed anhydride formation, by reacting the acid with an

acid chloride (e.g., isobutyl chloroformate or bis-(2-oxo-3-oxazolidinyl)-phosphinic chloride (Bop-Cl)) in the presence of a tertiary amine base (e.g., triethylamine) followed by treatment with the amine substrate.

Mesylate formation (Reaction Scheme II) may be carried out by treatment of the amine-alcohol substrate with methanesulfonyl chloride and triethylamine or pyridine or in an aprotic solvent, such as dichloromethane.

Base cyclization (Reaction Schemes II, VIII) may be carried out by treatment with a base (e.g., potassium t-butoxide or sodium hydride) in an inert solvent (e.g., dimethylformamide, tetrahydrofuran, dimethoxymethane, or toluene). Mitsunobu cyclization (Reaction Scheme II) may be carried out by procedures generally known in the art. See, e.g., R. K. Olsen, J. Org. Chem., 49, 3527 (1984); Genin, M. J., et al., J. Org. Chem., 58, 2334-7 (1993).

Alternatively, a mixture of compounds IV and VIII can be converted to compound Ia in a single pot by heating the mixture in a protic solvent (e.g., water, methanol, ethenyl or isopropanol or mixtures thereof) at 100 to 200 °C. See, e.g., European patent application 81 / 26,749, FR 2, 548,666 (1983).

Protection and deprotection (Reaction Schemes III, IV, V, XVI, XVIB, XIXB, XXI) may be carried out by procedures generally known in the art. See, for example, T. W. Greene, Protecting Groups in Organic Synthesis, Second edition, 1991. PG in Scheme V denotes a nitrogen-protecting group. One particularly useful group is tert-butoxy-carbonyl (BOC) which can be derived from the associated anhydride as shown in Scheme IV. BOC-protected amines may typically be

deprotected by treatment with acid (e.g., trifluoroacetic acid or hydrochloric acid) in procedures well understood by those having ordinary skill in the art.

Hydrogenolysis (Reaction Schemes III, IV, V) may be carried out with H_2 using a balloon apparatus or a Parr Shaker in the presence of a catalyst (e.g., palladium on activated carbon).

Amine alkylation and arylation (Reaction Schemes III, IV, V, IX, XII, XIXA, XIXB) may be carried out by methods known in the art. Suitable procedures are described in Cortizo, L., J. Med. Chem. 34, 2242-2247 (1991). For example, the alkylation or arylation may be carried out by treating the amine substrate with a halide (e.g., R^1-halo) or an oxytosylate (e.g., R^1-O-tosylate) in an aprotic solvent (e.g., dimethylformamide), optionally in the presence of a tertiary amine (e.g., triethylamine) or an inorganic base (e.g., potassium carbonate).

Reductive amination may be employed as an alternative to the foregoing amine alkylation and arylation procedures when R^1, R^6 or R^7 is $R^9R^{10}CH$- and R^9 and R^{10} are each independently hydrogen, alkyl, alkenyl, aryl, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl, or R^9 and R^{10} together are alkylene (i.e., $R^9R^{10}CH$- forms a cycloalkyl group). Such reductive amination may be carried out by treating the amine with (a) a ketone or aldehyde (R^9-C(O)-R^{10}), (b) $NaBH_4$, $NaBH_3CN$ or NaB(acetoxy)$_3$H, (c) a protic solvent (e.g., methanol) or a dipolar aprotic solvent (e.g., acetonitrile), and, optionally, (d) an acid (e.g., acetic acid, trifluoroacetic acid, hydrochloric acid, or titanium

isopropoxide). When R^1 is aryl or heteroaryl, transition metals (e. g., palladium or copper salts or complexes) may be used to promote the arylation reaction.

Alkylation of the isoindolone (Reaction Scheme X) may be carried out by treatment of the isoindolone with a strong base (i.e. sodium bis(trimethylsilyl)amide or lithium diisopropyl-amide) followed by an alkyl halide (e.g. R^8-halo) or alkyl sulfonate (e.g. R^8-tosylate) in an inert solvent (e.g. tetrahydrofuran or dimethoxy-ethane). Alternatively, as seen in Schemes X and XI, amine IVb can be treated under amide formation conditions with a ketone with the structure XB to provide a hydroxylactam XXV, which could be subjected to reduction conditions with such reducing agents as zinc in acetic acid or triethylsilane in trifluoroacetic acid to give IA^7.

Hydrazinolysis of phthalimides may be carried out by standard means known in the art. See, e.g., T. W. Greene, Protecting Groups in Organic Synthesis, Second edition, 1991.

Amide N-alkylation (Reaction Scheme VI) may be carried out by base treatment (e.g., NaH, KH, $KN[Si(CH_3)_3]_2$, K_2CO_3, P4-phosphazene base, or butyl lithium) in an aprotic organic solvent, followed by treatment with R^6-halo or R^6-O-tosylate. Use of P-phosphazene base is described in T. Pietzonka, D. Seebach, Angew. Chem. Int. Ed. Engl. 31. 1481, 1992.

Dehydration (Scheme VIII) may be carried out employing a strong acid such as hydrochloric acid, sulfuric acid or trifluoroacetic acid.

Hydrogenation (Scheme VIII) may be carried out in the presence of a conventional catalyst such as Pd/C or Pt or Rh under a H_2 atmosphere.

The addition reaction shown in Scheme IX may be carried out by treating IA^3 with an organometallic reagent XXIV, such as an organolithium or organic magnesium compound where organo is alkyl or aryl.

The deoxygenation or hydrogenation reaction (Scheme IX) is carried out in the presence of a strong acid such as trifluoroacetic acid or boron trifluoride etherate, in the presence of a hydride source such as triethyl silane or tris(trimethylsilyl)silane.

The alkylation in Schemes XIII, XIV, XVI, XVIA, XVIB is carried out in the presence of base such as butyllithium or sodium bis(trimethylsilyl)amide. It will be appreciated that R^{12} in $R^{12}Q$ may be any of the R^{12} groups as defined hereinbefore.

Alternatively, the alkylation in the above Schemes can be performed where either or both Z^1 or Z^2 is a bond, using a palladium catalyzed allylic alkylation procedure. In this reaction, the fluorenyl-type or indenyl-type precursors (compounds XXVIII, XXXVI, XXXVII, XXXIX, XL, XLVII) are reacted with a base (sodium hydride, sodium bis(trimethylsilyl)amide or bis(trimethylsilyl)-

acetamide), a palladium catalyst (for example $Pd(Ph_3)_4$) and an allylic acetate ($CH_3CO_2CH_2$-CH=CH- or CH_3CO_2CH(T)-CH=CH_2) in an inert solvent (for example THF). This reaction is to introduce either $-R^{12}$ (Scheme XII) or $-R^{11}-X^1$ (Schemes XIII, XIV, XVI, XVIA) or $-R^{11}$-OPG (Scheme XVIB, Scheme XXI). The product of this reaction contains either an $-R^{12}$ group or an $-R^{11}-X^1$ group (or an $-R^{11}$-OPG group) which begins with $-CH_2-CH=CH-$. Saturation of the alkene in R^{11} or R^{12} can be accomplished by standard catalytic hydrogenation conditions.

The sulfur oxidation in Schemes XIII, XVI and XVIII is carried out as follows.

Sulfides of structures XXXVI, XXXVIII, XXXIIIE and I^9 can be selectively oxidized to sulfoxides by 1 molar equivalent of reagents known in the art, such as 30% H_2O_2, $NaIO_4$, and peracids (e.g., meta-chloroperbenzoic acid). The resulting sulfoxides can be further transformed to corresponding sulfones by another molar equivalent or excess of 30% H_2O_2, $KMnO_4$, $KHSO_5$, or peracids (e.g., meta-chloroperbenzoic acid). Alternatively, the sulfones can be directly prepared from sulfides with 2 molar equivalents or more of oxidizing agents, such as 30% H_2O_2 and peracids (e.g., meta-chloroperbenzoic acid). In cases where an amine (such as a piperidine in I^9) is present during the oxidation, the basic nitrogen may be protected by pretreatment with an acid such as HCl or CF_3CO_2H (see Scheme XIX).

To prepare examples where Z^1 or Z^2 is -CHOH, the compounds I, Ii, II and IIi where Z^1 or Z^2 is C=O can be reduced with a hydride reagent, for example $NaBH_4$.

The compounds of the invention may be employed in preventing, stabilizing or causing regression of atherosclerosis in a mammalian species by administering a therapeutically effective amount of a compound to decrease the activity of MTP.

The compounds of the invention can be tested for MTP inhibitory activity employing the procedures set out in U.S. application Serial No. 117,362 filed September 3, 1993, employing MTP isolated from one of the following sources:

(1) bovine liver microsomes,

(2) $HepG_2$ cells (human hepatoma cells) or

(3) recombinant human MTP expressed in baculovirus.

The compounds of the invention may also be employed in lowering serum lipid levels, such as cholesterol or triglyceride (TG) levels, in a mammalian species, by administering a therapeutically effective amount of a compound to decrease the activity of MTP.

The compounds of the invention may be employed in the treatment of various other conditions or diseases using agents which decrease activity of MTP. For example, compounds of the invention decrease the amount or activity of MTP and therefore decrease serum cholesterol and TG levels, and TG, fatty acid and cholesterol absorption and thus are useful in treating hypercholesterolemia, hypertriglyceridemia, hyperlipidemia, pancreatitis, hyperglycemia and obesity.

The compounds of the present invention are agents that decrease the activity of MTP and can be administered to various mammalian species, such as monkeys, dogs, cats, rats, humans, etc., in need of

such treatment. These agents can be administered systemically, such as orally or parenterally.

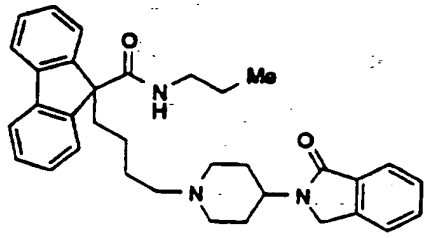
The agents that decrease the activity or amount of MTP can be incorporated in a conventional systemic dosage form, such as a tablet, capsule, elixir or injectable formulation. The above dosage forms will also include the necessary physiologically acceptable carrier material, excipient, lubricant, buffer, antibacterial, bulking agent (such as mannitol), anti-oxidants (ascorbic acid or sodium bisulfite) or the like. Oral dosage forms are preferred, although parenteral forms are quite satisfactory as well.

The dose administered must be carefully adjusted according to the age, weight, and condition of the patient, as well as the route of administration, dosage form and regimen, and the desired result. In general, the dosage forms described above may be administered in amounts of from about 5 to about 500 mg per day in single or divided doses of one to four times daily.

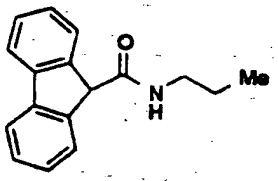
The following Examples represent preferred embodiments of the invention. All temperatures are in °C unless indicated otherwise.

Example 1

9-[3-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]propyl]-N-propyl-9H-fluorene-9-carboxamide



A.

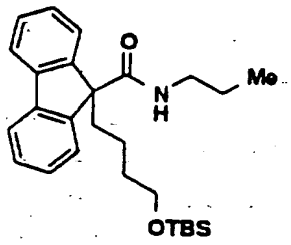


To a suspension of 10 g (47.57 mmol) of 9-fluorenecarboxylic acid (Aldrich) in 80 mL of CH_2Cl_2, under argon at 0°C, was added a catalytic amount of DMF (0.5 mL) followed by the dropwise addition of 36 mL (71.35 mmol) of oxalyl chloride (2M in CH_2Cl_2). The reaction was warmed to RT and was stirred for 45 min (the reaction becomes a clear yellow solution) at which time it was evaporated to dryness and pumped on under high vacuum for 0.5 h. The yellow residue was dissolved in 50 mL of CH_2Cl_2, cooled to 0°C, and treated dropwise with 7.8 mL (95.14 mmol) of propylamine(very exothermic) followed by 7 mL of pyridine to sponge up excess HCl. The reaction solidified and was treated with 1:1 CH_2Cl_2/water (200 mL) and allowed to stir until everything was in solution. The organics were washed with water (2x), dried ($NaSO_4$) and evaporated to provide a yellow

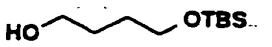
solid. Purification by crystallization from hot methanol resulted in 4.0 g (33%) of title compound as a pale yellow solid.

mp 198-200°C.

B.



B(1).



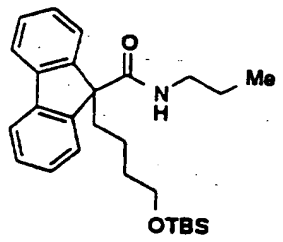
To a solution of 49 mL (0.55 mol) of 1,4-butanediol in 25 mL of DMF, under argon at 0°C, was added 10.5 g (0.15 mol) of imidazole followed by 20.7 g (0.14 mol) of t-butyldimethylsilyl chloride. The reaction was slowly warmed to RT and stirred for 18 h at which time the reaction was diluted with ether and washed with NH_4Cl, water, Na_2CO_3, brine and dried ($MgSO_4$). The resulting colorless title compound in the form of a liquid, 50 g, contained approximately 15% of the disilylated compound.

B(2).

To a solution of 8.5 g (42 mmol) of Part B(1) compound in 50 mL of THF, under argon at 0°C, was added 7.3 g (108 mmol) of imidazole and 16.7 g (64 mmol) of triphenylphosphine. This mixture was stirred for 45 min (solution became homogeneous at

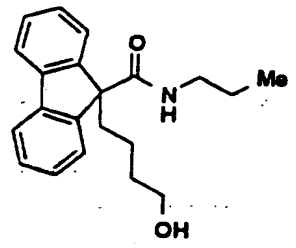
which time 16.2 g (64 mmol) of iodine in 50 mL of THF was added dropwise over 20 min. The reaction was stirred for 1 h, diluted with hexanes and washed with 1M sodium bisulfite, Na_2CO_3, brine and dried (Na_2SO_4). The resulting residue was triturated with ether (3x), filtered (to remove triphenylphosphine oxide) and evaporated to provided 10 g (61%) of title compound as a pale yellow oil.

B(3).



To a mixture of 300 mg (1.20 mmol) of Part A compound in 10 mL of THF, under argon at 0°C, was added dropwise 960 mL (2.40 mmol) of n-BuLi (2.5 M in hexanes). The resulting orange dianion was stirred at 0°C for 0.5 h at which time 452 mg (1.44 mmol) of Part B(2) compound was added dropwise. The reaction was warmed to RT and was stirred for 18 h at which time it was treated with a 1:1 mixture of ethyl acetate/water. The organics were dried (Na_2SO_4), evaporated and flash chromatographed on 50 g of silica gel eluting with 4:1 hexanes/ ethyl acetate to provide 460 mg (87%) of title compound as a pale yellow solid.

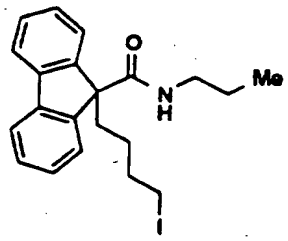
C.



To 5.6 g (12.80 mmol) of Part B compound was added 14.1 mL (14.10 mmol) of 1M tetrabutylammonium fluoride in THF. The reaction was stirred, under argon at RT, for 18 h at which time it was diluted with ether and quenched with NH_4Cl. The organics were washed with water, brine, dried (Na_2SO_4) and evaporated. Flash chromatography was performed on 250 g of silica gel eluting with 95:5 dichloromethane/isopropanol to provide 4.09 g (99%) of title compound as a white solid.

mp 73-75°C.

D.



To a solution of 1 g (3.10 mmol) Part C compound in 20 mL of THF, under argon at 0°C, was added 463 mg (6.81 mmol) of imidazole followed by 1.0 g (4.03 mmol) of triphenylphosphine. The mixture became homogeneous after 15 min at which time 1.0 g (4.03 mmol) of iodine in 20 mL of THF was added dropwise over 20 min. The reaction was warmed to RT

and was stirred for 1 h at which time it was diluted with hexanes and the organics were washed with sodium bisulfite, $NaHCO_3$, brine and dried (Na_2SO_4). Flash chromatography was performed on 100 g of silica gel eluting with 1:1 hexanes/ethyl acetate to provide 1.1 g (85%) of title compound as a colorless oil.

E. 2-[1-(Phenylmethyl)-4-piperidinyl]-1H-isoindol-1,3(2H)-dione

A mixture of phthalic anhydride (15.0 g, 101 mmol) and 4-amino-1-benzylpiperidine (19.3 g. 101 mmol) was heated with stirring in an oil bath until the mixture melted (about 125°C). The reaction was kept at this temperature until the mixture solidified again (about 30 minutes). The reaction was cooled to room temperature. Purification was performed by flash chromatography on 1 kg silica gel, loaded and eluted with 30% ethyl acetate in hexane. Pure fractions were combined and evaporated to give compound A (25 g, 77%) as a white solid, melting point 151-154°C.

F. 2,3-Dihydro-2-[1-(phenylmethyl)-4-piperidinyl]-1H-isoindol-1-one

To a solution of compound E (20.0 g, 62.5 mmol) in acetic acid (248 mL) was added zinc dust (28.6 g, 438 mmol) under argon. With mechanical stirring, the reaction was refluxed overnight. The reaction was filtered through Celite®, then evaporated to dryness. Dichloromethane (500 mL) was added, and the organic layer was washed with saturated sodium bicarbonate (2 x 100 mL), brine (100 mL) and dried over $MgSO_4$. Evaporation gave a crude oil. The resulting residue was azeotroped with

toluene (2 x 30 mL) to afford a white solid. The product was recrystallized from isopropanol to give compound B (16 g, 80%) as a white solid (melting point 130-133°C).

G. 2-(4-Piperidinyl)-2,3-dihydro-1H-isoindol-1-one

To a solution of Part F compound (8.5 g, 26.4 mmol) in ethanol (65 mL) was added acetic acid (3.5 mL, 52.8 mmol), followed by 10% palladium on activated carbon (0.7 g) under argon. The slurry was purged with nitrogen and agitated under a pressure of 45 psi of hydrogen gas for 48 hours. The reaction mixture was filtered through Celite® and washed with ethanol. The filtrate was evaporated to dryness. The resulting residue was dissolved in chloroform (100 mL) and washed with 1 N KOH saturated with sodium chloride (2 x 30 mL) and dried over $MgSO_4$. The resulting clear solution was evaporated to dryness and azeotroped with toluene (2 x 30 mL) to give compound G (5.0 g, 77%) as a white solid, melting point 137-140°C.

H. 9-[3-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]propyl]-N-propyl-9H-fluorene-9-carboxamide

To a solution of 330 mg (0.76 mmol) of Part D compound in 5 mL of DMF, under argon at RT, was added 210 mg (1.52 mmol) of K_2CO_3 followed by 198 mg (0.76 mmol) of Part G compound. The mixture was stirred at RT for 72 h, at which time the reaction was diluted with ether and washed with water, brine, dried (Na_2SO_4) and evaporated. Recrystallization was

attained from hot hexanes to provide 270 mg (68%) of title compound as a white solid.

mp 136-138°C.

Anal. Calcd. for $C_{34}H_{39}N_3O_2$:
C, 78.28; H, 7.53; N, 8.05
Found: C, 78.11; H, 7.62; N, 8.09.

Example 1A

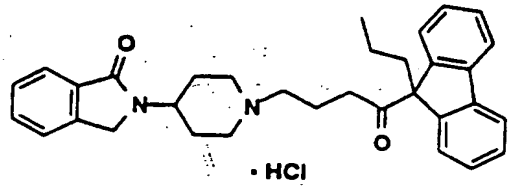
Alternate synthesis of Example 310 hydrochloride salt

To a solution of Example 5 free amine (12 g, 23.1 mmol) in absolute EtOH (400 mL) was added 10% palladium on activated carbon (1.2 g). The mixture was hydrogenated on a Parr apparatus at 40 psi for 2 h, then filtered through Celite. The filtrate was concentrated in vacuo to provide a colorless oil. The product was dissolved in MeOH (100 mL) and 1.0M HCl in Et_2O (20 mL, 20 mmol) was added dropwise. The reaction was stirred for 10 min then concentrated in vacuo. The residue was taken up in CH_3CN (2 mL) and water (25 mL) was added. The slightly cloudy solution was lyophilized overnight to give title compound (11.1 g, 86%) as a white lyophilate.

Analysis Calcd. for $C_{34}H_{39}N_3O_2 \cdot 1.3HCl \cdot 1.6H_2O$:
C, 68.24; H, 7.33; N, 7.02; Cl, 7.76
Found: C, 68.27; H, 7.31; N, 6.99; Cl, 7.77.

Example 2

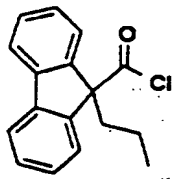
2,3-Dihydro-2-[1-[4-oxo-4-(9-propyl-9H-fluoren-9-yl)butyl]-4-piper-idinyl]-1H-isoindol-1-one, monohydrochloride



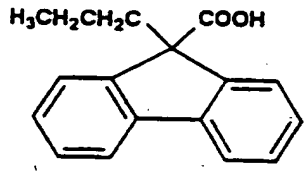
A.

To a stirred solution of 28.55 g (301.9 mmol) of 3-chloro-1-propane (Aldrich) in 300 mL of THF at -20°C under argon was added 101 mL (303 mmol) of 3.0 M methyl magnesium chloride in THF dropwise over 20 min. After 0.5 h at -20°C, the reaction was allowed to warm to room temperature and 11.0 g (452.8 mmol) of magnesium turnings were added and the reaction was heated to reflux. At the start of reflux, 0.60 mL (6.94 mmol) of 1,2-dibromoethane was added and after 1 h at reflux another 0.60 mL was added. After 2 h at reflux the reaction was allowed to cool to room temperature.

B.



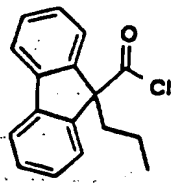
B(1). 9-Propyl-9H-fluorene-9-carboxylic acid



A solution of 9-fluorenecarboxylic acid (12 g, 57 mmol) in 250 ml of THF was cooled to 0°C under an argon atmosphere and 2 equiv. (71.25 ml) of a 1.6 **M** n-butyl lithium solution in hexane was added followed by the addition of n-propyl iodide (7.5 ml, 13.1 g, 77 mmol). The reaction mixture was stirred at 0°C for 6 hrs. An additional 1 ml of n-propyl iodide was added and the reaction stirred for 4 hrs at 0°C. The reaction was quenched by adding 75 ml of water and the pH was adjusted to pH 1 with 3 **N** HCl. The reaction mixture was extracted with hexane (3x200ml) and the hexane extract washed with water, brine and dried over anhy. sodium sulfate. The solvents were evaporated yielding the crude product as a yellow oil which was dissolved in ~250 ml of ethanol and heated at reflux with Darco G-60, filtered through Celite and concentrated to approximately one half of the original volume. Water was slowly added until the mixture became cloudy. The mixture was reheated and slowly allowed to cool to room temperature yielding 10.5 grams (73%) of title compound as colorless crystals.

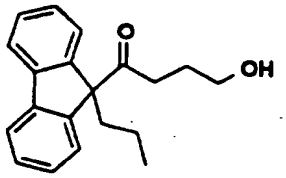
m.p.120-122°C.

B(2).



A solution of oxalyl chloride (4.5 mL, 8.93 mmol) was added over 5 min. to a solution of Part B(1) compound in CH_2Cl_2 (10 mL) containing 2 drops of DMF. The reaction was stirred at RT for 2 h, then concentrated in vacuo to give 1.6 g of the crude acid chloride as a dark yellow solid.

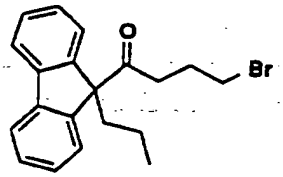
C.



A solution of Part B compound (1.07 g, 3.97 mmol) in THF (10 mL) under argon was cooled to 0°C. Copper (I) iodide (38 mg, 0.20 mmol) was added followed by dropwise addition of Part A compound (14.5 mL, 0.3M in THF, 4.37 mmol) over 10 min. Upon addition, a deep red color appeared but quickly dissipated with stirring. The opaque yellow reaction was stirred at 0°C for 45 min, then quenched by addition of saturated NH_4Cl (10 mL). The reaction was diluted with water (10 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were washed with saturated NH_4Cl, water, and brine (10 mL each), then dried over $MgSO_4$. Evaporation gave 1.3 g of a yellow oil, which was purified by flash chromatography on silica gel (150 g), loading in 50%

EtOAc/hexane, and eluting with 25% EtOAc/hexane to provide title compound (885 mg, 76%) as a colorless oil.

D.



N-Bromosuccinimide (431 mg, 2.42 mmol) was added to a solution of Part C compound (647 mg, 2.20 mmol) and triphenylphosphine (634 mg, 2.42 mmol) in CH_2Cl_2 (7 mL) at 0°C under argon. The reaction was stirred at 0°C for 1 h, diluted with CH_2Cl_2 (20 mL), and washed with 10% aqueous potassium sulfite (5 mL), water (5 mL), and brine (5 mL), then dried over $MgSO_4$. The mixture was filtered, and to the filtrate was added silica gel (3 g). Evaporation gave a green powder, which was purified by flash chromatography on silica gel (50 g) eluting with 30% CH_2Cl_2/hexane to provide title compound (733 mg, 93%) as a colorless oil.

E. 2,3-Dihydro-2-[1-[4-oxo-4-(9-propyl-9H-fluoren-9-yl)butyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

A solution of Part D compound (336 mg, 0.941 mmol) and Example 1 Part G compound (225 mg, 1.04 mmol) in absolute ethanol (3 mL) was refluxed under argon overnight (20 h) and cooled to RT, at which time a white solid precipitated. The mixture was concentrated in vacuo, and the resulting residue was partitioned between EtOAc (20 mL) and saturated

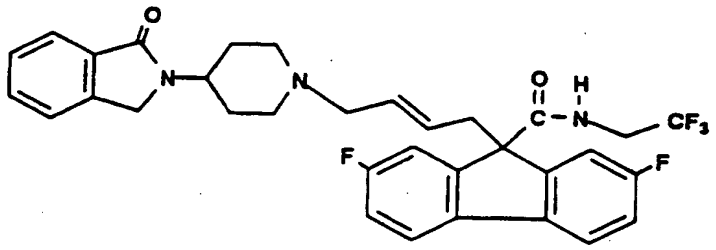
$NaHCO_3$ (10 mL). The organic layer was washed with water (5 mL) and brine (5 mL), then dried over Na_2SO_4. Evaporation gave 415 mg of a colorless oil, which was purified by flash chromatography on silica gel (50 g) eluting with 25% acetone/CH_2Cl_2 to give 205 mg of the desired free amine as a colorless oil.

To a solution of the amine prepared above in Et_2O (3 mL) was added 1N HCl/Et_2O (3 mL, 3 mmol). The mixture containing a gummy solid was concentrated in vacuo to give a gummy glass. The product was dissolved in isopropanol (2 mL) and hexane (15 mL) was added to precipitate the product. The mixture was concentrated in vacuo to give a foamy solid, which was dried at 60°C overnight under high vacuum to give title compound (206 mg, 41%) as a white foam.

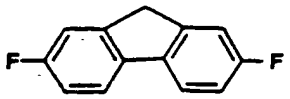
Anal. Calcd. for $C_{33}H_{37}ClN_2O_2 \cdot H_2O$:
C, 72.27; H, 7.19; N, 5.11; Cl, 6.46
Found: C, 72.36; H, 7.21; N, 5.02; Cl, 6.59.

Example 3

(E)-9-[4-[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]-2-butenyl-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



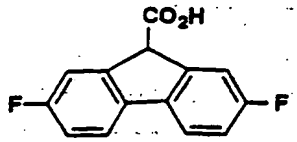
A.



To a THF (25 ml) supension of 2,7-diamino-fluorene (Aldrich) (7.17 g, 0.036 mol) at -10°C under argon was added aqueous HBF_4 (71 mL, 1.13 mol, 48-50%). Near the end of addition stirring became difficult due to solid formation, although most of the solid went into solution upon complete addition of acid. A saturated aqueous solution of sodium nitrite (7.1 g in 11 mL, 0.103 mol) was added and after 1.5 h the mixture was filtered, washing with 5% aq. HBF_4, MeOH, then ether, and the collected solid dried briefly on the fliter flask. The resulting brown solid (9.7 g) was used in the subsequent reaction.

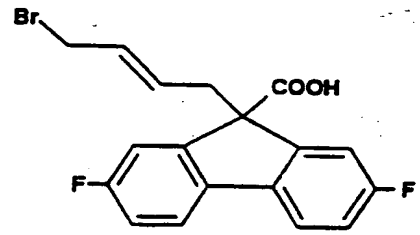
The above solid was suspended in xylenes (100 ml) and heated to 110°C for 2 h, with gas evolution observed, then brought to reflux for an additional 2 h. The solution was decanted from a black tar in the reaction flask and the volatiles removed under high vacuum to give a dark tan solid (7.5 g). The solid was crystallized from hot EtOH to give title compound (1.4 g) as a colorless solid. An ether wash of the black tar was combined with the mother liquor and concentrated in vacuo. The oily-solid residue (4.3 g) was purified by flash column chromatography (SiO_2, 9 by 16 cm), eluting with hexanes then 2.5% EtOAc:hexanes, to give title compound (2.44 g, total 3.84 g, 52% yield) as a colorless solid.

B.



To a THF (15 ml) solution of Part A compound (1.38 g, 6.82 mmol) at -5°C (ice/brine bath) under argon was added dropwise n-BuLi (3.4 ml, 8.50 mmol, 2.5 M in hexanes). After 1.15 h, crushed solid CO_2 (excess) was added, followed by Et_2O (~5 ml), and the reaction allowed to stir at room temperature for 19 h. The brown colored reaction mixture was cooled to 0°C, quenched with 2N HCl, and the aqueous layer extracted twice with EtOAc. The combined organics were dried over Na_2SO_4 and evaporated *in vacuo* to give crude title compound (1.64 g), as a colorless solid suitable for the next reaction. Trituration with hexanes can remove unreacted starting material Part A compound.

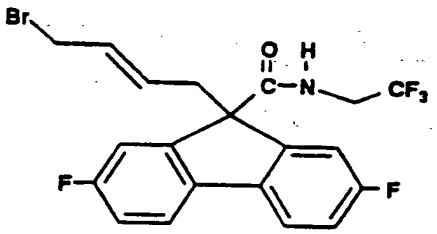
C.



A solution of Part B compound (2,7-difluorofluorene-9-carboxylic acid) (500mg, 2.05 mmol) in 5 ml of THF was cooled to -30°C under an argon atmosphere and 2 equiv. of a 2.5 M solution of n-butyl lithium in hexane (1.64 ml, 4.1 mmol) was added. The mixture was stirred for 5 min. at -30°C and was then added to a cold (-30°C) solution of 1,4-

dibromo-2-butene (2.14 g, 10 mmol) in 4 ml of THF. The reaction mixture was stirred at -30°C for 30 min and was then quenched with 1 N HCl and extracted with ethyl acetate (3x10 ml). The ethyl acetate extract was washed with water, brine and dried over anhy. sodium sulfate. The crude material was purified on a Merck EM silica column eluting with 5% isopropanol/dichloromethane yielding 480 mg (62%) of title compound as a colorless solid, m.p. 142-146°C.

D.

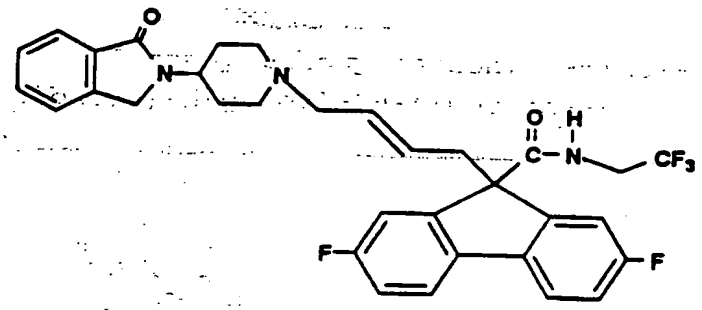


The Part C carboxylic acid (465 mg, 1.23 mmol) was dissolved in 10 ml of dichloromethane and DMF (50 ml) was added. The mixture was cooled to 0°C under an argon atmosphere and oxalyl chloride (165 mg, 1.3 mmol) was added and the mixture allowed to warm to ambient temperature and stir for 2.5 hrs. The mixture was evaporated several times from dichlormethane yielding the crude acid chloride as a pale yellow solid.

The acid chloride was dissolved in 5 ml of THF and cooled to 0°C under an argon atmosphere. Triethylamine (142 mg, 1.4 mmol) was added followed by the addition of 2,2,2-trifluoroethyl-amine (139 mg, 1.4 mmol). The reaction was allowed to warm to ambient temperature and stir overnight. The reaction was quenched by adding sat. sodium bicarbonate and extracted with ethyl acetate (3x20 ml). The crude

product was purified on a Merck EM silica column eluting wiith 10% ethyl acetate / hexane yielding 230 mg (38%) of title compound as a pale yellow solid.

E.



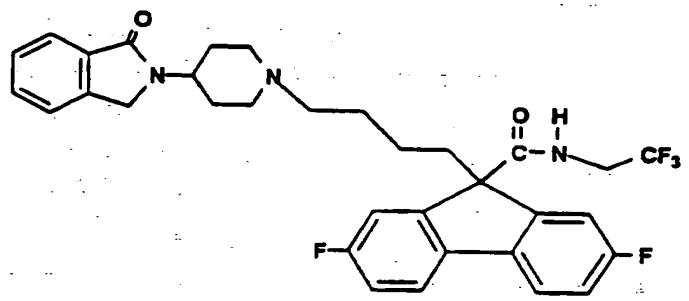
A solution of Part D compound (184 mg, 0.4 mmol) in dimethylformamide (3 ml) was stirred under an argon atmosphere and potasssium carbonate (55 mg, 0.4 mmol) was added, followed by the addition of Example 1 Part G compound (95 mg, 0.44 mmol) and the resulting mixture was stirred overnight at ambient temper-ature. The reaction was diluted with ethyl acetate and washed with water, brine and dried over anhy. sodium sulfate. The solvents were evaporated and the crude residue was purified on a Merck EM silica column eluting with 5% isopropanol/dichloromethane yielding 230 mg (96%) of title compound as a colorless solid.

Anal Calc'd for $C_{33}H_{30}N_3F_5O_2 + 1.7\ H_2O$:
C, 63.35; H, 5.37; N, 6.72; F, 15.18
Found: C, 63.24; H, 5.34; N, 6.45; F, 15.14.

m.p. 168-170°C.

Example 4

9-[4-[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide



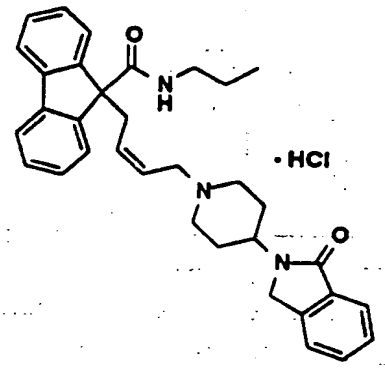
A solution of Example 3 compound (100 mg, 0.17 mmol) in 2 ml of DMF and 2 ml of methanol containing 30 mg of 10% palladium on carbon was stirred under a hydrogen atmosphere (balloon) for 18 hrs. The reaction was filtered through a 0.2 mm nylon filter to remove the catalyst and the solvent evaporated yielding the crude product as a colorless oil. The product was purified on a Merck EM silica column eluting 5% IPA / dichloromethane yielding 91 mg (90%) of title compound as a colorless solid.

m.p. 150-152°C.

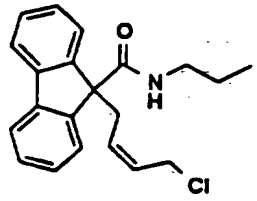
Anal Calc'd for $C_{33}H_{32}N_3F_5O_4$ + 1.75 H_2O:
C, 63.01; H, 5.69; N, 6.68; F, 15.10
Found: C, 63.05; H, 5.50; N, 6.48; F, 14.99.

Example 5

(Z)-9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide, monohydrochloride



A.



Butyllithium (8.4 mL, 2.5M in hexane, 21 mmol) was added dropwise over 10 min to a solution of fluorenecarboxylic acid (Aldrich Chemical Co.) (2.10 g, 10 mmol) in THF (50 mL) at 0°C under argon. During addition of the first equivalent of BuLi, the reaction became thick with a white precipitate which became yellow and cleared after addition of the second equivalent. The reaction was stirred at 0°C for 20 min, then *cis*-1,4-dichloro-2-butene (1.2 mL, 11 mmol) was added dropwise over 5 min. The reaction lightened in color during addition and was stirred at 0°C for 3 h, then poured into 1N HCl (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined

organic layers were washed with brine (30 mL) then dried over $MgSO_4$. Evaporation provided 3.5 g of a yellow oil containing crystalline solid. The crude residue was triturated with hexane (20 mL). The supernatant was decanted, and the residue pumped under high vacuum to give 2.93 g of a tan solid.

To a suspension of the crude acid prepared above (1.42g, 4.77 mmol) and N,N-dimethylformamide (5 drops) in CH_2Cl_2 (15 mL) at RT under argon was added oxalyl chloride (3.6 mL, 2.0M in CH_2Cl_2, 7.16 mmol). The reaction bubbled for 10 min, then the reaction was stirred at RT for 1.5 h, at which time all solids had dissolved. The reaction was concentrated in vacuo to give an orange oil. The crude acid chloride was dissolved in CH_2Cl_2 (15 mL) and cooled to 0°C. Propylamine (1.2 mL, 14.3 mmol) was added dropwise over 1 min, and the reaction was stirred at 0°C for 10 min. The reaction was partitioned between EtOAc (50 mL) and water (20 mL). The organic layer was washed with 1N HCl (2 x 20 mL) and brine (20 mL), then dried over $MgSO_4$. Evaporation gave 1.7 g of an orange oil, which was purified by flash chromatography on silica gel (150 g) eluting with CH_2Cl_2 to give title compound (1.38 g, 84%) as a pale yellow oil.

B. 9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide, monohydrochloride

A mixture of Part A compound (440 mg, 1.30 mmol) and Example 1 Part G compound (337 mg, 1.56 mmol) in DMF (3 mL) under argon was heated at 50°C overnight, cooled to RT, then the solvent was distilled off under high vacuum at RT. The residue

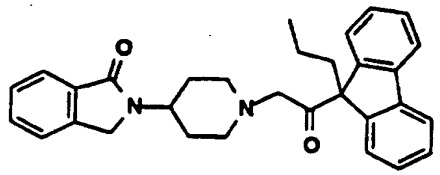
was partitioned between CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (7 mL). The organic layer was washed with brine (5 mL) and dried over Na_2SO_4. Evaporation gave 900 mg of a pale yellow oil, which was purified by flash chromatography on silica gel (75 g) eluting with 3% MeOH/CH_2Cl_2 to afford 467 mg of the free base as a white foam.

The free amine prepared above was dissolved in MeOH (3 mL) and treated with 1N HCl/Et_2O (3 mL), then concentrated in vacuo. The resulting foam was heated at 50°C under high vacuum overnight then for 6 h further at 60°C to give title compound (420 mg, 58%) as a white foamy solid.

Anal. Calcd. for $C_{34}H_{38}ClN_3O_2 \cdot 0.7H_2O$:
C, 71.81; H, 6.98; N, 7.39; Cl, 6.23.
Found: C, 71.86; H, 7.34; N, 7.34; Cl, 6.16.

Following the procedure of Examples 1 to 5, the following additional compounds were prepared.

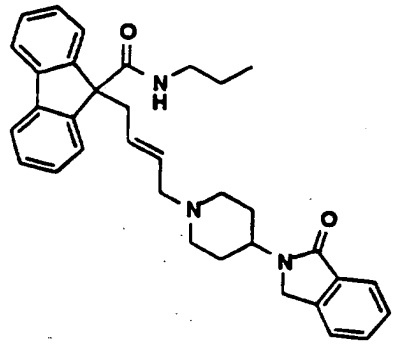
6. 2,3-Dihydro-2-[1-[2-oxo-2-(9-propyl-9H-fluorene-9-yl)ethyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride



MS (ES) 465 (M+H)
mp 146-149°C

Anal. Calcd. for $C_{31}H_{33}ClN_2O_2 \cdot 0.95\ H_2O$:
Calcd: C, 71.85; H, 6.79; N, 5.41
Found: C, 72.29; H, 7.22; N, 5.37.

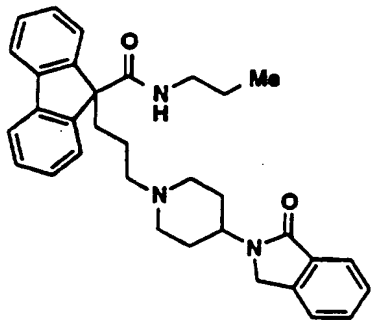
7. (E)-9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide, monohydrochloride



MS(Cl) 520 (M+H)
mp 115-116.5°C

Anal. Calcd. for $C_{34}H_{37}N_3O_2$
Calcd: C, 78.58; H, 7.18; N, 8.09
Found: C, 78.49; H, 7.26; N, 8.06.

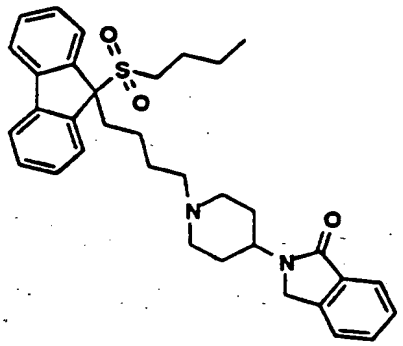
8. 9-[3-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]propyl]-N-propyl-9H-fluorene-9-carboxamide



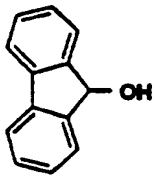
M.S. (ES, + ions) m/e 508 (M+H)
mp 172-175°C

Calcd: C, 78.07; H, 7.34; N, 8.28
Found: C, 77.80; H, 7.50; N, 8.10.

Example 9

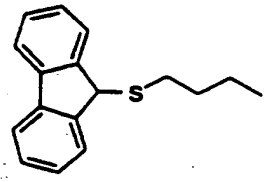


A.



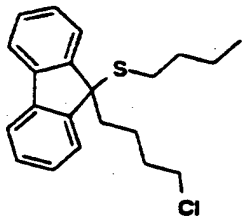
The title compound was purchased from Aldrich Chemical Co.

B.



A solution of Part A alcohol (1.58 g, 10.0 mmol) and butanethiol (0.72 g, 8.00 mmol) in 10 mL of dichloromethane at -20°C was treated with boron triflouride etherate (1.28 g, 9.00 mmol). The reaction was stirred for 1 h at -20°C and warmed to room temperature. After stirring for 18 h the reaction was concentrated in vacuo, and the crude product was purified by column chromatography on silica gel (100 g) with hexanes followed by 1:9 dichloromethane/hexanes to give 1.54 g (75%) of title compound as a colorless oil.

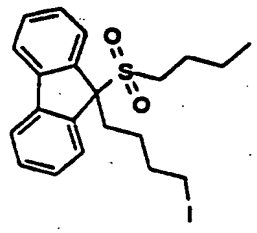
C.



A solution of Part B compound (1.0 g, 3.93 mmol) in 10 mL of THF at -78°C was treated with n-butyllithium in hexanes (1.75 mL, 4.40 mmol) followed by 1-chloro-4-bromo-butane (0.81 g, 4.70 mmol). The reaction was stirred for 0.5 h and warmed to room temperature for 18 h. The reaction was diluted with 30 mL of aqueous NH_4Cl solution and 30 mL of ethyl acetate. The organic fraction was dried (Na_2SO_4) and concentrated. The crude product was purified by

column chromatography on silica gel (50 g) with 2:98 acetone/dichloromethane (500 mL) followed by 15:85 dichloromethane/hexanes to give 1.00 (73%) of title compound as a colorless oil.

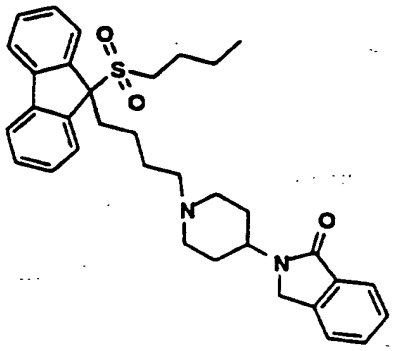
D.



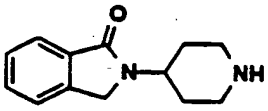
To a solution of Part C sulfide (0.30 g, 0.86 mmol) in dichloromethane (5 mL) at 0°C was added 3-chloroperoxybenzoic acid (0.37 g, 80% by weight = 0.1.72 mmol) in one portion. The mixture was stirred for 1 h then partitioned between 0.1 M K_2CO_3 (20 mL) and ether (30 mL). The organic fraction was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel (50 g) with 15:85 ethyl acetate/hexanes to give 0.24 g of sulfone as a colorless oil.

To a solution of the sulfone chloride (0.24 g, 0.64 mmol) in 2-butanone (10 mL) at RT was added sodium iodide (1.00 g, 6.66 mmol) in one portion. The mixture was refluxed for 30 h when it was diluted with water (20 mL) and ether (30 mL). The organic fraction was dried (Na_2SO_4) and concentrated. The crude product was purified by column chromatography on silica gel (50 g) with 15:85 ethyl acetate/hexanes to give 0.24 g (81%) of title compound as a colorless oil.

E.



To a stirred solution of 0.70 g (1.49 mmol) of Part D compound in 6 mL of DMF at RT was added 0.38 g (1.80 mmol) of



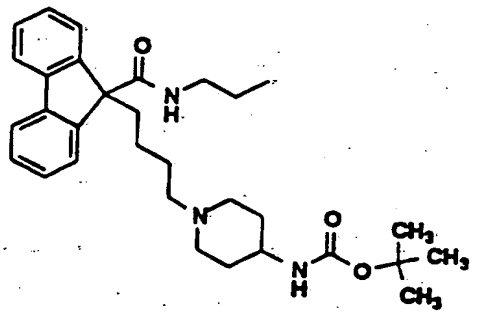
(prepared as described in Example 1 Part G). The reaction mixture was warmed to 55° and allowed to stir for 24 h. The mixture was diluted with $NaHCO_3$ solution (50 mL) and ethyl acetate (50 mL). The layers were separated, the organics dried (Na_2SO_4) and concentrated. The remainder was purified by flash column chromatography on silica gel (100 g) eluting with 5:95 methanol/dichloromethane (700 mL) followed by 5:95:0.5 methanol/dichloromethane/NH_3 (1L). Pure fractions were pooled and concentrated to give 0.70 g (85%) of title compound as a thick oil which solidified after standing.

m.p. 128-131°C.

Anal. calcd for $C_{34}H_{40}N_2O_3S \cdot 0.45\ H_2O$:
C, 72.29; H, 7.30; N, 4.96; S, 5.76
Found: C, 72.25; H, 7.15; N, 5.00; S, 5.69.

Example 10

9-[4-[4-[[(1,1-Dimethylethoxy)carbonyl]amino]-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide



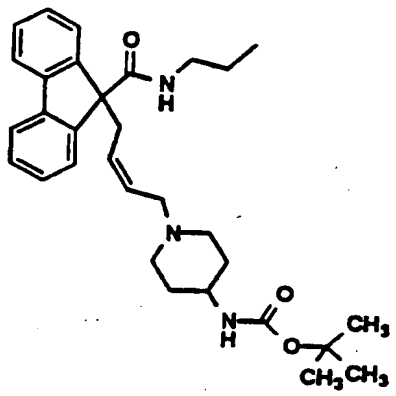
A. [1-(Phenylmethyl)-4-piperidinyl]carbamic acid, 1,1-dimethylethyl ester

To a solution of 4-amino-1-benzylpiperidine (20.0 g, 105 mmol) in dichloromethane (150 mL) was added dropwise a solution of di-tert-butyldicarbonate (25.2 g, 116 mmol) in dichloromethane (50 mL) at 0°C. After addition, the reaction was warmed to room temperature. The reaction was maintained at this temperature for 2 hours. The reaction was evaporated to dryness. The resulting residue was recrystallized from ethyl ether to give compound A (23.5 g, 76%) as a white solid (melting point 119-121°C).

B. 4-Piperidinylcarbamic acid, 1,1-dimethylethyl ester

A suspension of 64.94 g (0.224 mol) of compound A and 25.6 mL (0.447 mol) of acetic acid in 500 mL of absolute ethanol was warmed to dissolve all solids. After cooling, 6.5 g (1 wt %) of 10% palladium on charcoal was added and the mixture was shaken on a Parr apparatus under initial hydrogen pressure of 40 psi for 23 hours. The catalyst was removed by filtration and the solution was concentrated to a clear oil which was dissolved in 1.5 L of chloroform. The organics were washed with a 3 N KOH solution saturates with NaCl (2 x 75 mL). The aqueous layer was back extracted with chloroform (5 x 200 mL). The combined organics were dried (sodium sulfate) and concentrated to provide 65 g of a white solid which was redissolved in 1.5 L of chloroform and washed with brine (2 x 200 mL) to remove residual acetate. The combined aqueous layers were back extracted and the combined organics were dried (sodium sulfate) and concentrated to provide 40.15 g (90%) of compound B as a white solid (melting point 156-159°C).

C.



The solution of Example 5 Part A compound (6.0 g, 17.6 mmol) and Part B compound (2.88 g, 16.0 mmol) in DMF (3mL) was stirred at 50°C overnight. Ethyl acetate (150 mL) was added and the organic layer was washed with saturated sodium bicarbonate solution (2 x30 mL), water (2 x 50 mL), brine (2 x 50 mL) and dried over $MgSO_4$. Purification was performed by flash chromatography on silica gel (300 g), loaded and eluted with 2.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give title compound(3.0 g, 34%) as a colorless oil.

D. 9-[4-[4-[[(1,1-Dimethylethoxy)carbonyl]-amino]-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide

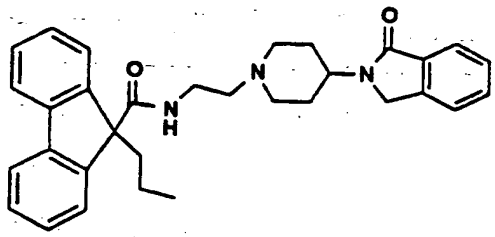
To a solution of Part C compound (3.0 g, 5.89 mmol) in methanol (10 mL) at RT was added palladium on activated carbon (10%, 300 mg). The reaction was hydrogenated (balloon) at RT for 18 h. The reaction was filtered and the filtrate was evaporated to give a white solid. The resulting solid was recrystallized from ethyl acetate/hexane to give title compound (2.90 g, 97%) as a white solid.

m.p. 118-120 °C.

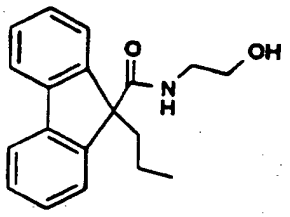
Anal. Calc. for $C_{31}H_{43}N_3O_3 \cdot 2.4\ H_2O$:
C, 67.83; H, 8.78; N, 7.65
Found: C, 67.45; H, 8.33; N, 7.52

Example 11

N-[2-[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]ethyl]-9-propyl-9H-fluorene-9-carboxamide



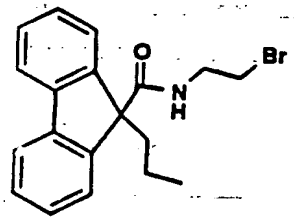
A.



To a CH_2Cl_2 (30 ml) solution of Example 2 Part B(1) compound (2 g, 7.93 mmol) under nitrogen was added 1,1'-carbonyldiimidazole (1.35 g, 8.32 mmol). After 1 h, ethanolamine (0.486 g, 7.95 mmol) was added, followed by DMF (1.5 mL) to aid solubility of the amine, and the reaction allowed to stir at room temperature overnight. After 24 h, the reaction mixture was diluted with saturated $NaHCO_3$ and the aqueous layer extracted twice with CH_2Cl_2. The combined organics were washed with H_2O, dried over

Na_2SO_4 and evaporated *in vacuo* to give an oily residue (2.55 g). The residue was purified by flash column chromatography (SiO_2, 350 mL), eluting with 30% EtOAc:CH_2Cl_2, to give title compound (1.73 g, 74% yield) as a colorless solid.

B.



To a CH_2Cl_2 (30 ml) solution of Part A compound (1.4 g, 4.74 mmol) at 0°C under argon was added triphenylphosphine (1.39 g, 5.30 mmol) and N-bromosuccinimide (0.930 g, 5.22 mmol) and the reaction allowed to stir for 2 h. The reaction mixture was diluted with CH_2Cl_2 and the poured into 10% aqueous sodium bisulfite. The aqueous layer was extracted 4 times with CH_2Cl_2, the combined organics dried over Na_2SO_4, and evaporated *in vacuo* to give an oily brown colored residue (3.4 g). The residue was purified by flash column chromatography (SiO_2, 5 by 18.5 cm), eluting with 4:1 CH_2Cl_2:hexanes to give title compound (1.52 g, 89.5% yield) as a colorless solid.

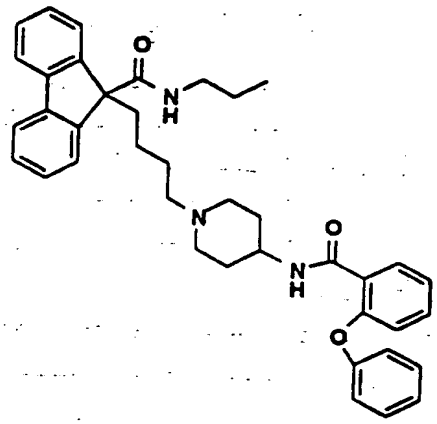
C. N-[2-[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]ethyl]-9-propyl-9H-fluorene-9-carboxamide

A DMF (1.5 ml) solution of Part B compound (520 mg, 1.45 mmol) and Example 1 Part G compound (315 mg, 1.45 mmol) under argon was stirred for 1h, followed by the addition of K_2CO_3 (200 mg, 1.45 mmol) and DMF (0.5 ml). After 24 h, the reaction was partitioned between saturated $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc, $CHCl_3$, and twice with CH_2Cl_2. The combined organics were dried over Na_2SO_4 and the volatiles were removed *in vacuo* to give an oily-solid residue (720 mg). The residue was purified by flash column chromatography (SiO_2, 5 by 8 cm), eluting with 1% MeOH:CH_2Cl_2 then 5% MeOH:CH_2Cl_2, to give title compound (184 mg, 25% yield) as a colorless solid. mp 219-221°C.

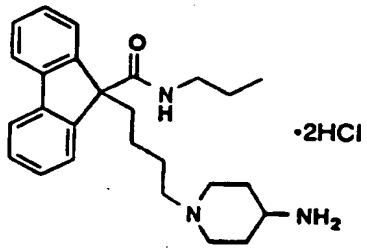
Anal. Calc. for $C_{32}H_{35}N_3O_2 \cdot 0.32\ H_2O$:
C, 76.97 H, 7.19; N 8.42
Found: C, 76.88; H, 7.16; N, 8.51.

Example 12

9-[4-[4-[[2-(Phenoxyphenyl)carbonyl]amino]-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide



A.



To a solution of Example 10 Part A compound (2.65 g, 5.20 mmol) in dioxane (10 mL) at RT was added a solution of hydrochloric acid in dioxane (4N, 10 mL, 40 mmol). The reaction was stirred at RT for 3.5 h. The reaction was evaporated to give a white solid. The resulting solid was recrystallized from methanol/water to give title compound (2.4 g, 97%) as a white solid.

m.p. 156-160°C.

Anal. Calc. for $C_{26}H_{37}Cl_2N_3O \cdot 1.1\ H_2O$:
C, 62.67; H, 7.93; N, 8.43
Found: C, 62.63; H, 7.87; N, 8.46.

B. 9-[4-[4-[[2-(Phenoxyphenyl)carbonyl]-amino]-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide

To a solution of 2-phenoxybenzoic acid (purchased from Aldrich) (500 mg, 2.33 mmol) and DMF (1 drop) in dichloromethane (10 mL) at RT was added dropwise a solution of oxalyl chloride in dichloromethane (2.0M, 1.28 mL, 2.56 mmol). Bubbling of escaping gasses continued for 10 min after addition. The reaction was stirred at RT for 60 min, then concentrated in vacuo to give a crude oil. To a solution of crude acid chloride and triethylamine (1.14 mL, 8.16 mmol) in dichloromethane (10 mL) at 0 °C under argon was added dropwise a solution of Part A compound (1.12 g, 2.33 mmol) in dichloromethane (2 mL). The reaction was stirred at 0 °C for 30 min. Ethyl acetate (100 mL) was added to dilute the reaction and the resulting solution was washed with H_2O (2 x 30 mL), brine (2 x 30 mL) and dried over $MgSO_4$. Evaporation gave a crude gum. Purification was performed by flash chromatography on silica gel (100 g), loaded and eluted with 2.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give a coloress gum. The resulting product was triturated with ethyl ether to give title compound (720 mg, 51%) as a white solid.

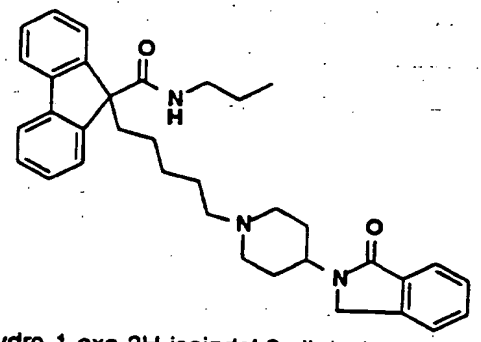
m.p. 149-152°C.

Anal. Calc. for $C_{39}H_{43}N_3O_3 \cdot 0.2\ H_2O$:
C, 77.38; H, 7.23; N, 6.94
Found: C, 77.37; H, 7.39; N, 6.89.

Examples 13 to 20

Following the procedures set out in Examples 1 to 12, the following compounds of the invention were prepared.

13.



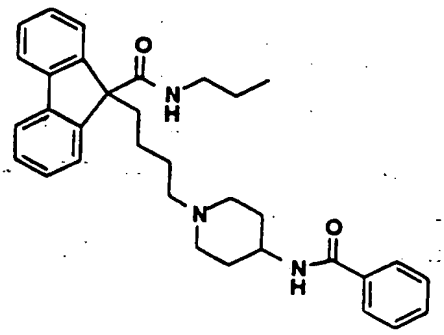
9-[5-[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]pentyl]-N-propyl-9H-fluorene-9-carboxamide.

m.p. 146-148°C

MS (ES, + ION): 536 (M+H)

Anal. Calcd. for $C_{35}H_{42}ClN_3O_2 \cdot 1.8\ H_2O$:
C, 69.76; H, 7.29; N, 6.97; Cl, 5.88
Found: C, 69,70; H, 7.39; N, 7.00; Cl, 5.74.

14.



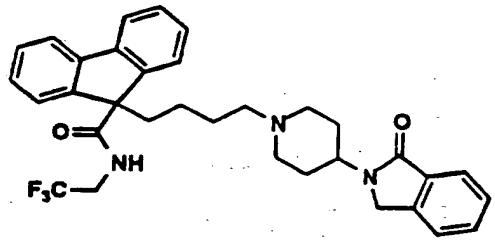
9-[4-[4-(Benzoylamino)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide.

m.p. 157-160°C

MS (Cl, + ion) (M+H) 510

Anal. Calcd. for $C_{33}H_{39}N_3O_2 \cdot 0.5\ H_2O$:
C, 76.41; H, 7.77; N, 8.10
Found: C, 76.37; H, 7.70; N, 8.02.

15.



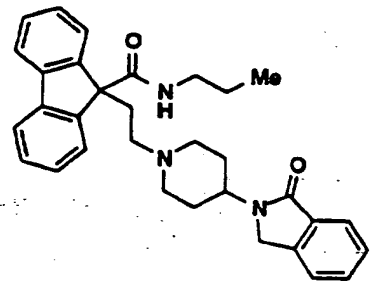
9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

m.p. 143-146°C

MS (ES, + ions) m/z 562 (M+H)

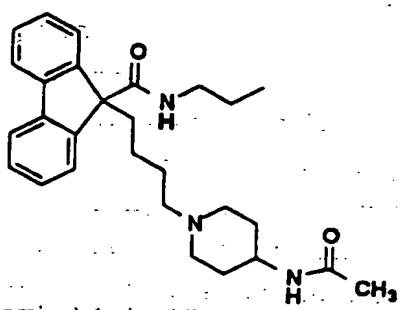
Anal. Calcd. for $C_{33}H_{34}N_3F_3O_2$:
C, 70.57; H, 6.10; N, 7.48; F, 10.15
Found: C, 70.04; H, 6.18; N, 7.34; F, 9.87.

16.



9-[2-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]ethyl]-N-propyl-9H-fluorene-9-carboxamide, monohydrochloride.

17.



9-[4-[4-(Acetylamino)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide.

m.p. 133-135°C

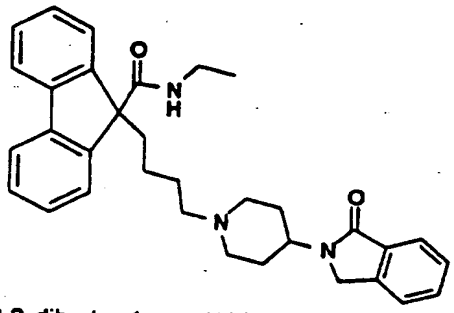
MS (Cl, + ion) (M+H) 448

Anal. Calcd. for $C_{28}H_{37}N_3O_2 \cdot 1.0\ H_2O$:

C, 72.23; H, 8.44; N, 9.02

Found: C, 71.94; H, 7.90; N, 8.88.

18.



N-Ethyl-9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide

m.p. 137-140°C

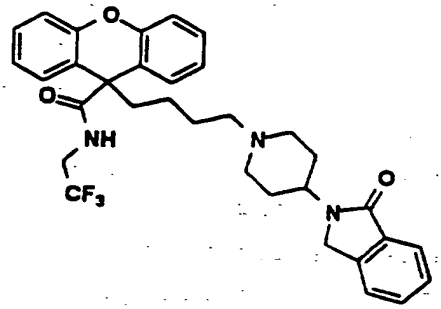
MS (Cl, $M+H^+$) m/z 508+

Anal. Calcd. for $C_{33}H_{37}N_3O_2 \cdot 0.29\ H_2O$:

C, 77.27; H, 7.39; N, 8.19

Found: C, 77.05; N, 7.38; N, 8.41.

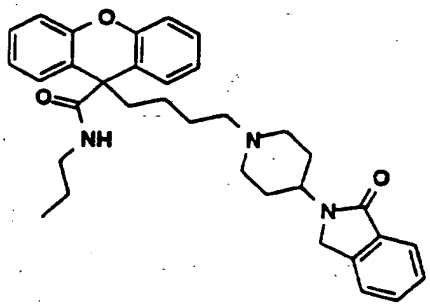
19.



9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-2,2,2-trifluoroethyl-9H-xanthene-9-carboxamide.

m.p. 164-166°C (dec)
M.S. (FAB) m/z 578 (M+H)

20.

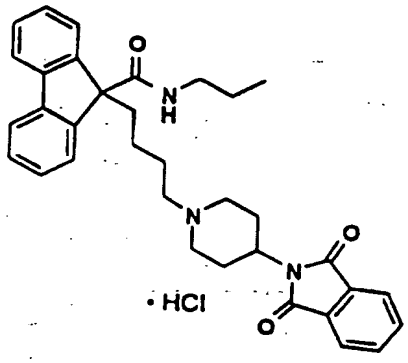


9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-xanthene-9-carboxamide.

m.p. 62-65°C
Anal. Calcd. for $C_{34}H_{39}O_3N_3+0.5\ H_2O$:
C, 74.70; H, 7.37; N, 7.69
Found: C, 74.45; H, 7.32; N, 7.56

Example 21

9-[4-[4-(2,3-Dihydro-1,3-dioxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, monohydrochloride



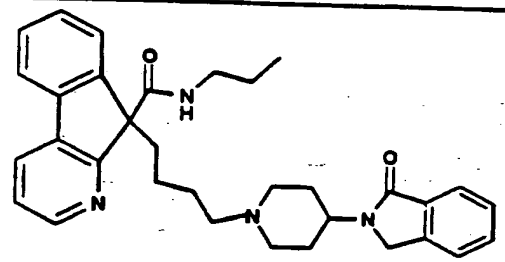
A solution of Example 12 Part A compound (500 mg, 1.05 mmol), diisopropylethylamine (0.4 mL, 2.31 mmol) and phthalic anhydride (170 mg, 1.15 mmol) in toluene (3 mL) was refluxed for 5 h, then cooled to RT. Dichloromethane (80 mL) was added and the solution was washed with water (2 x 30 mL), brine (2 x 30 mL) and dried over $MgSO_4$. Purification was performed by flash chromatography on silica gel (50 g), loaded and eluted with 2.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give a white solid. The resulting product was dissolved in ethyl ether (5 mL) and a solution of hydrochloric acid in ethyl ether (0.77M, 2.0 mL) was added. The reaction was stirred at RT for 10 min, then evaporated to dryness. The product was dried in a vacuum oven (50 °C, 18 h) to give title compound (440 mg, 73%) as a white solid.

m.p. 125-130°C

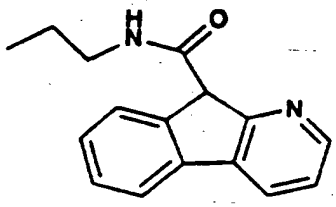
Anal. Calc. for $C_{34}H_{38}ClN_3O_3 \cdot 1.3\ H_2O$:
C, 68.57; H, 6.87; N, 7.06; Cl, 5.95
Found: C, 68.71; H, 6.66; N, 7.01; Cl, 5.82.

Example 22

9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-indeno[2,1-b]-pyridine-9-carboxamide

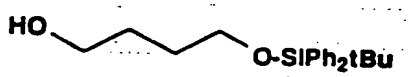


A.

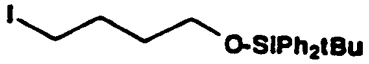


A THF (5 ml) solution of 1-aza-fluorene (233 mg, 1.39 mmol; prepared from benzo(f)quinoline by known procedures, Kloc, K. *Journal f. prakt. Chemie*, 319, 959-967 (1977) and Kloc, K. *Heterocycles*, 9, 849-852 (1978)) and *n*-propyliso-cyanate (0.13 ml, 1.39 mmol) was degassed three times by cooling to -78°C, evacuating, and allowing to warm to room temperature, and finally purging with argon. To the degassed solution at -10°C was added dropwise sodium bis(trimethylsilyl)amide (1.4 ml, 1 M in THF). After 5 min, a second portion of *n*-propylisocyanate (0.13 ml, 1.39 mmol) was added to the red solution. The now green colored reaction mixture was quenched after

a further 15 min with saturated NH_4Cl. The aqueous layer was extracted with EtOAc, the organics washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give a red colored oily-solid residue (535 mg). The residue was purified by flash column chromatography (SilicAR® buffered silica gel, 5 by 7 cm), eluting with 20% EtOAc:CH_2Cl_2, and flushing with 5% MeOH:CH_2Cl_2 to give title compound (202 mg, 58% yield) as an orange colored solid. mp 131-133°C.

B. 

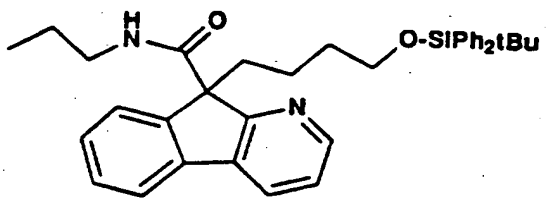
To a THF (100 ml) suspension of sodium hydride (4 g, 60% oil dispersion, 0.10 mol) at 18°C (cool water bath) under argon is added 1,4-butane-diol. After stirring at room temperature for 14 h, t-butylchlorodiphenylsilane (26 mL, 0.1 mol) was added in rapid drops. The reaction was quenched after 30 min with H_2O and the aqueous layer was extracted with hexanes. The organic layer was dried over Na_2SO_4 and evaporated to an oil (33 g). The residue was purified by flash column chromatography (silica gel, 10 by 26 cm), eluting with CH_2Cl_2, 5, 7.5, and then 10% EtOAc:CH_2Cl_2 to give title compound (24.5 g, 74%) as a colorless oil.

C. 

To a THF (70 ml) solution of Part B compound (5.48 g, 0.0167 mol), triphenylphosphine (4.3 g, 0.0164 mol), and imidazole (2.49g, 0.0366 mol) at 0°C was added a THF (15 ml) solution of iodine (4.23 g, 0.0167 mol) over 10 min. After 1 h at room temperature, the reaction was cooled to 0°C and

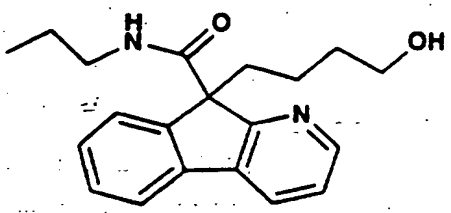
quenched with 5% aqueous sodium bisulfite. The mixture was diluted with H_2O and hexanes, the organic layer washed with H_2O, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and evaporated to an oily-solid. The residue was triturated with hexanes, cooled to 0°C, filtered and the volatiles removed in vacuo to give an oil (7.35 g). This residue was purified by flash column chromatography (SilicAR™ buffered silica gel, 5 by 10 cm), eluting with 30% CH_2Cl_2:hexanes to give title compound (6.2 g, 84%) as a colorless oil.

D.



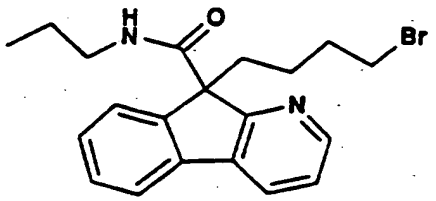
A THF (9 ml) solution of Part A compound (400 mg, 1.58 mmol) was degassed three times by cooling to -78°C, evacuating, and allowing to warm to room temperature, and finally purging with argon. To the degassed solution at 0°C was added dropwise n-BuLi (1.3 ml, 2.5 M in hexanes). After several minutes, Part C compound (0.63 ml, 1.82 mmol) was added to the red solution. The now brown colored reaction mixture was quenched after a further 1 h with saturated NH_4Cl. The aqueous layer was extracted twice with EtOAc, the organics dried over Na_2SO_4, and evaporated *in vacuo* to give an orange colored oil (1.07 g). The residue was purified by flash column chromatography (SilicAR™ buffered silica gel, 5 by 8.5 cm), eluting with 8% EtOAc:CH_2Cl_2 to give title compound (817 mg, 92%) as a colorless oil.

E.



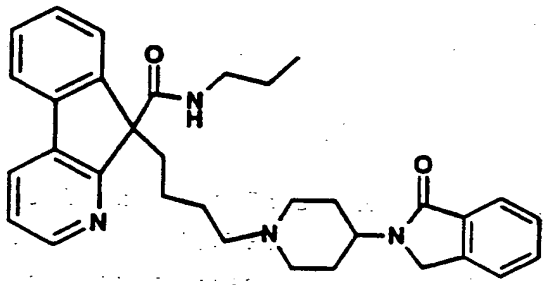
To a THF (3.5 ml) solution under argon of Part D compound (800 mg, 1.42 mmol) was added dropwise tetrabutylammonium fluoride (1.5 ml, 1 M in THF). After 2 h, a second portion of tetra-butylammonium fluoride (0.15 ml, 1 M in THF) was added and the reaction mixture was allowed to stir a further 1 h. The reaction mixture was partitioned between H_2O and EtOAc. The aqueous layer was extracted 3 times with EtOAc, and the organics washed with brine. The first organic layer contained less ammonium salts and was dried over Na_2SO_4, and evaporated *in vacuo* to give an oil (885 mg). The residue was purified by flash column chromatography (SilicAR" buffered silica gel, 90 g), eluting with 4.5% MeOH:CH_2Cl_2 to give title compound (437 mg, 95%) as a colorless oil.

F.



To a CH_2Cl_2 (5 ml) solution of Part E compound (231 mg, 0.712 mmol) and triphenylphos-phine (285 mg, 1.09 mmol) at 0°C under argon was added N-bromosuccinimide (153 mg, 0.860 mmol). After 2.15 h, a second portion of N-bromosuccinimide (18 mg, 0.101 mmol) was added and the reaction stirred 45 min at 0°C and 15 min at room temperature. The reaction mixture was then quenched with 10% sodium bisulfite and the aqueous layer extracted twice with CH_2Cl_2. The combined organics were washed with brine, dried over Na_2SO_4, and evaporated *in vacuo* to give an oily-solid residue (653 mg). The residue was purified by flash column chromatography (SilicAR" buffered silica gel, 68 g), eluting with 10.5% EtOAc:CH_2Cl_2 to give the unstable title compound (217 mg, 78%) as a colorless oil.

G.



To a DMF (1.6 ml) solution of Part F compound (180 mg, 0.465 mmol) and Example 1 Part G compound

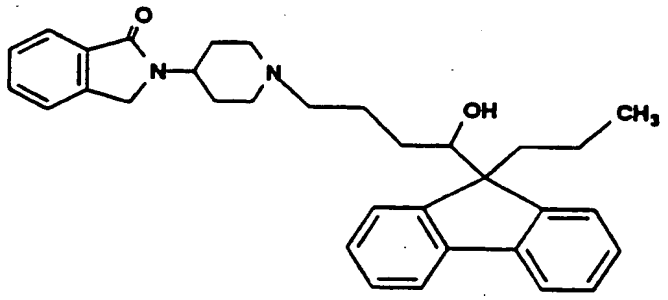
(135 mg, 0.624 mmol) under argon was added K_2CO_3 (65 mg, 0.47 mmol). After 18.15 h, the purple colored reaction was partitioned between dilute $NaHCO_3$ and EtOAc. The aqueous layer was extracted twice with EtOAc, the combined organics were washed with H_2O, brine, dried over Na_2SO_4, and the volatiles were removed *in vacuo* to give a purple colored oil (230 mg). The residue was purified by flash column chromatography (SilicAR® buffered silica gel, 26.5 g), eluting with 5 then 6% MeOH:CH_2Cl_2, to give title compound (83 mg, 34% yield) as a colorless foam. Additional title compound was obtained as a mixture (96 mg, 92% pure by HPLC, 72% yield)

mp 52-54°C.

MS: (electrospray, $M+H^+$): m/z 523^+.

Example 23

2,3-Dihydro-2-[1-[4-hydroxy-4-(9-propyl-9H-fluoren-9-yl)butyl]-4-piperidinyl]-1H-isoindol-1-one



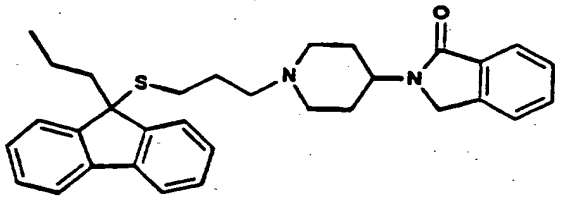
A solution of Example 2 Part D free amine (300 mg, 0.61 mmol) in 12 ml of methanol was cooled to 0°C under an argon atmosphere and 2 equiv. of sodium borohydride (48.5 mg, 1.28 mmol) was added. The reaction mixture was stirred at 0°C for 45 min. The reaction was quenched with 1 N hydrochloric acid and

extracted with ethyl acetate (3 x 20 ml). The extract was washed with brine and dried over sodium sulfate. Evaporation yielded an oily residue which was dissolved in dichloromethane, dried over sodium sulfate and evaporated to yield 550 mg of a colorless solid. The crude product was purified on a Merck EM silica column eluting with 5% methanol/dichloromethane yielding 290mg (96%) of title compound as colorless solid.

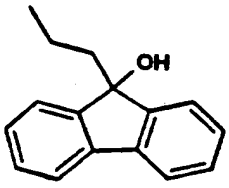
m.p. 75 - 78°C.
MS(CI) m/z 495 (M+H).

Example 24

2,3-Dihydro-2-[1-[3-[(9-propyl-9H-fluoren-9-yl)-thio]propyl]-4-piperidinyl]-1H-isoindol-1-one



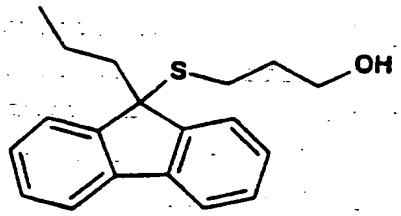
A.



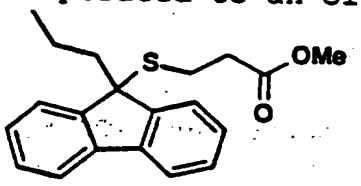
To a THF (100 ml) solution of fluoren-9-one (9.12 g, 0.051 mol) at -10°C under argon was added dropwise n-propylmagnesium chloride (25.4 ml, 2 M in ether). After 1.15 h, the orange colored reaction mixture was quenched with saturated NH_4Cl. The

aqueous layer was extracted twice with EtOAc, the organics washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give an oily-solid residue (11.1 g). The residue was purified by crystallization from EtOH:H_2O to give title compound contaminated with 14% by weight 9-hydroxyfluorene (4 g, 30% yield) as a colorless solid. Material was sufficiently pure for the subsequent reaction.

B.



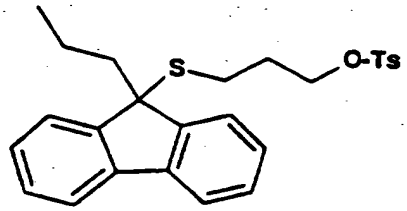
To an AcOH (25 ml) solution of Part A compound (3.64 g, 0.014 mol) and methyl 3-mercaptopropionate (1.62 ml, 0.015 mol) under argon is added concentrated H_2SO_4 (7 drops). After stirring at room temperature for 24 h, the reaction was concentrated to 1/3 the original volume and diluted with H_2O. The aqueous layer was extracted with EtOAc and the organic layer washed with 1 N NaOH. The basic wash was extracted 3 times with EtOAc, the combined organics extracted with brine, dried over Na_2SO_4 and evaporated to an oily-solid of the structure (B1)



(5.55 g). (Compound B(1) was sufficiently pure for the subsequent reaction. Rf = 0.49 (25% EtOAc:hexanes).

To an EtOH (15 ml) solution of compound B(1) (385 mg, 0.956 mmol) was added $NaBH_4$ (470 mg, 0.012 mol). After stirring overnight, the reaction mixture was cooled to 0°C and quenched with saturated NH4Cl. The aqueous layer was extracted with EtOAc, the organic layer washed with brine, dried over Na_2SO_4 and evaporated to an oily residue (390 mg). This residue was purified by flash column chromatography (silica gel, 3 by 10 cm), eluting with 3% EtOAc:CH_2Cl_2 to give title compound (110 mg, 38% yield from Part A compound) as a colorless oil.

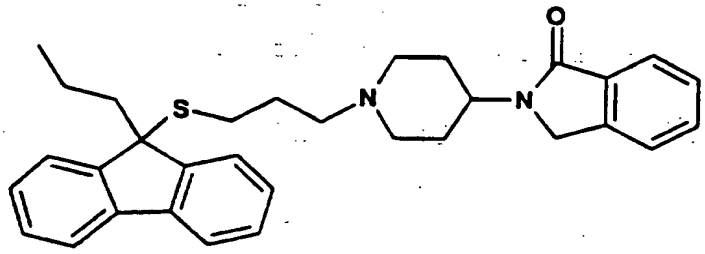
C.



To a pyridine (0.75 ml) solution of Part B compound (110 mg, 0.369 mmol) at 0°C was added *p*-toluenesulfonyl chloride (80 mg, 0.42 mmol) and the reaction slowly allowed to come to room temperature. After 4 h and 7.5 h, more *p*-toluenesulfonyl chloride (60 and then 40 mg, 0.52 mmol) was added at room temperature and the reaction was stirred at 5°C overnight. A final portion of *p*-toluenesulfonyl chloride (40 mg, total 1.15 mmol) was then added and the reaction stirred at room temperature for 8 h. The reaction mixture was partitioned between EtOAc and saturated $NaHCO_3$. The aqueous layer was extracted 3 times with EtOAc, the organic layer washed with brine, dried over Na_2SO_4 and evaporated to an oily-solid (200 mg). This residue was preabsorbed onto Celite and purified by flash column

chromatography (silica gel, 3 by 8 cm), eluting with 15% EtOAc:hexanes to give title compound (110 mg, 66% yield) as a colorless oil.

D.

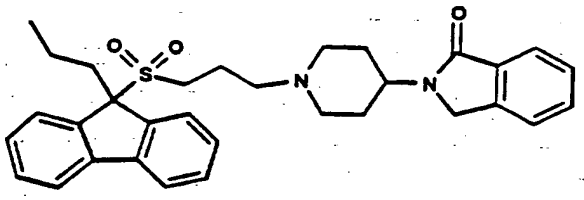


A mixture of Part C compound (102 mg, 0.227 mmol), Example 1 Part G compound (64 mg, 0.296 mmol), and K_2CO_3 (34 mg, 0.246 mmol) in isopropanol (1.5 ml) under argon was refluxed for 6 h. After cooling, the reaction was partitioned between saturated $NaHCO_3$ and EtOAc. The aqueous layer was extracted twice with EtOAc, the combined organics were dried over Na_2SO_4 and the volatiles were removed *in vacuo* to give an oil (126 mg). The residue was combined with another crude residue from an identical reaction using 48.6 mmol of Part C compound (146 mg total). The mixture was purified by flash column chromatography (silica gel, 3 by 5.5 cm), eluting with 4% MeOH:CH_2Cl_2 to give impure title compound (108 mg). The mixture was further purified by flash column chromatography (silica gel, 12 g), eluting with 4% MeOH:CH_2Cl_2 to give title compound (101 mg, 74% yield) as an oily foam.

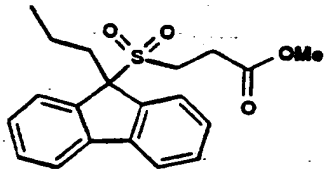
MS: (electrospray, M+H$^+$): m/z 497$^+$.
Anal. Calcd. for $C_{32}H_{36}N_2OS \cdot 0.26\ H_2O$:
C, 76.64; H, 7.34; N, 5.59
Found: C, 76.73; H, 7.27; N, 5.51.

Example 25

2,3-Dihydro-2-[1-[3-[(9-propyl-9H-fluoren-9-yl)-sulfonyl]propyl]-4-piperidinyl]-1H-isoindol-1-one



A.

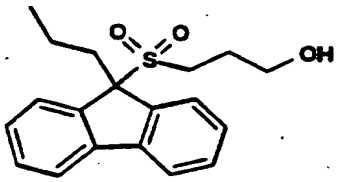


To an AcOH (25 ml) solution of Example 24 Part A compound (3.64 g, 0.014 mol) and methyl 3-mercaptopropionate (1.62 ml, 0.015 mol) under argon is added concentrated H_2SO_4 (7 drops). After stirring at room temperature for 24 h, the reaction was concentrated to 1/3 the original volume and diluted with H_2O. The aqueous layer was extracted with EtOAc and the organic layer washed with 1 N NaOH. The basic wash was extracted 3 times with EtOAc, the combined organics extracted with brine, dried over Na_2SO_4 and evaporated to an oily-solid (5.55 g, > 100% recovery).

To a CH_2Cl_2 (25 ml) solution of crude compound prepared above (1 g, 2.63 mmol) at 0°C under argon was added 3-chloroperoxybenzoic acid (1.41 g, 6.13 mmol, 75%) and the reaction brought to room temperature. After 1.45, 4.1, and 6 h, more 3-chloroperoxybenzoic acid (0.25, 0.3, and 0.2 g, total 9.39 mmol) was added. The reaction was stored at -80°C after 8 h. After warming, the reaction mixture was partitioned between 1 N NaOH and EtOAc. The aqueous layer was extracted twice with EtOAc, the organic layer washed with brine, dried over Na_2SO_4 and evaporated to an oily-solid residue. This residue was purified by flash column chromatography (silica gel, 5 by 9 cm), eluting with 18% EtOAc:hexanes to give title compound (630 mg, 67% yield from Example 24 Part A compound) as a colorless solid. mp 74-77°C.

Anal. Calc. for $C_{20}H_{22}SO_4 \cdot 0.29\ H_2O$:
C, 66.04; H, 6.26; S, 8.81
Found: C, 66.04; H, 6.11; S, 8.45.

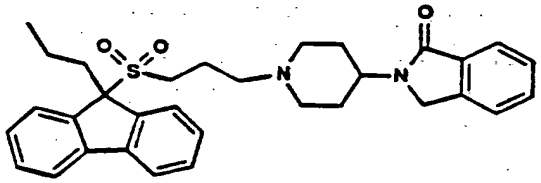
B.



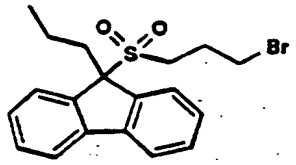
To an EtOH (14 ml) suspension of Part A compound (559 mg, 1.56 mmol) at 0°C under argon was added $NaBH_4$ (80 mg, 3.36 mmol) and the mixture brought to room temperature. After 1 h, the reaction mixture was cooled to 0°C and a second portion of $NaBH_4$ (80 mg, 3.36 mmol) was added. After 5 h at room temperature, the reaction mixture was quenched

at 0°C with saturated NH_4Cl and the mixture stirred at room temperature for 30 min. The aqueous layer was extracted twice with EtOAc and the combined organic layers were evaporated to an oily residue. This residue was co-evaporated 3 times with MeOH to give 500 mg of oily-solid. After pre-absorbing onto Celite, the residue was purified by flash column chromatography (silica gel, 5 by 7 cm), eluting with 3% MeOH:CH_2Cl_2 to give title compound (328 mg, 64% yield) as a colorless solid. mp 111.5-112.5°C.

C.



To a CH_2Cl_2 (5 ml) solution of Part B compound (308 mg, 0.933 mmol) and triphenylphosphine (490 mg, 1.87 mmol) at 0°C under argon was added N-bromosuccinimide (210 mg, 1.18 mmol). After 2 h, a second portion of N-bromosuccinimide (40 mg, 0.34 mmol) was added and the reaction stirred an additional 1 h. The reaction mixture was then quenched with 10% sodium bisulfite and the aqueous layer extracted twice with EtOAc. The combined organics were washed with H_2O, brine, dried over Na_2SO_4, and evaporated *in vacuo* to give an oily-solid residue. The residue was purified by flash column chromatography (SilicAR" buffered silica gel, 5 by 9 cm), eluting with 6.7% hexanes:CH_2Cl_2, then CH_2Cl_2 to give the unstable Compound C(1) of the

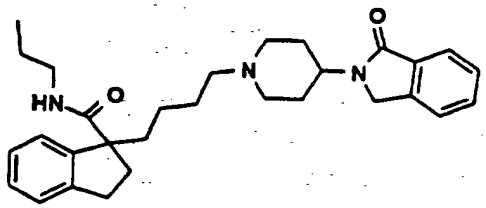


structure (283 mg, 77% yield) as a colorless solid. mp 83-86°C.

A DMF (2 ml) solution of Compound C(1) (234 mg, 0.595 mmol) and Example 1 Part G compound (155 mg, 0.717 mmol) under argon was stirred for 15 h. A second portion of Example 1 Part G compound (17 mg, 0.078 mmol) was then added, followed in 4 h by K_2CO_3 (33 mg, 0.239 mmol). After 24 h, the cooled reaction mixture was partitioned between saturated $NaHCO_3$ and EtOAc. The aqueous layer was extracted with EtOAc, the organics were washed with brine, dried over Na_2SO_4 and the volatiles were removed *in vacuo* to give an oil (357 mg). The mixture was purified by flash column chromatography (silica gel, 3 by 12.5 cm), eluting with 5% MeOH:CH_2Cl_2 to give impure title compound (222 mg), as well as pure title compound (76 mg, contaminated with 10% DMF). The pure title compound was crystallized from EtOAc:hexanes to give title compound (39 mg) as a colorless solid. The impure title compound was further purified by flash column chromatography (silica gel, 24 g), eluting with 5% MeOH:CH_2Cl_2 to give title compound (153 mg, 192 mg total, 61% yield). mp dec. 138-141°C. MS: (electrospray, $M+H^+$): m/z 529^+.

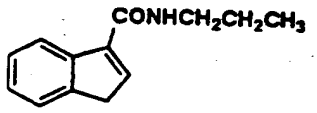
Anal. Calcd. for $C_{32}H_{36}N_2O_3S \cdot 1.01\ H_2O$:
C, 70.29; H, 7.01; N, 5.12
Found: C, 70.45; H, 6.60; N, 4.96.

Example 26

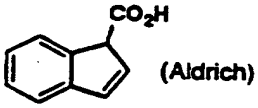


2,3-Dihydro-1-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-1H-indene-1-carboxamide

A.



To a stirred slurry of



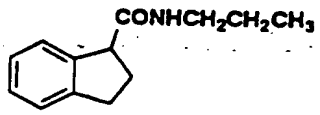
(Aldrich)

(3.20 g, 20.0 mmol) in 20 mL of dichloromethane at room temperature under argon was added 15.0 mL of oxalyl chloride solution (30.0 mmol, 2 M in dichloromethane) and then 0.1 mL of DMF. Vigorous gas evolution results in a light yellow solution. After 1 h, the reaction mixture was evaporated at less than 25°C and the residue was dissolved in 10 mL of THF.

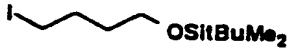
This solution was then added dropwise over 15 minutes to a solution of 3.5 mL of n-propylamine (46 mmol) in 25 mL of THF at -10°C under argon. After one hour, the reaction mixture was partitioned

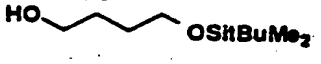
between ethyl acetate and 10% citric acid solution. The organic extract was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5 x 20 cm column, 1:2 ethyl acetate/hexanes as elutant) provided title compound as a yellow solid, 2.36 g, 59% yield, mp 123-125°C.

B.



A degassed slurry of Part A compound (1.10 g, 5.47 mmol) and 330 mg of 10% palladium-on-carbon in 25 mL of ethyl acetate at room temperature was stirred under atmospheric pressure hydrogen for 16 h. The reaction was filtered through Celite and evaporated to give title compound as a white solid, 894 mg, 81% mp 61-63°C.

C. 

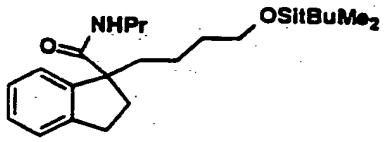
To a solution of 49 mL (0.55 mol) of 1,4-butanediol in 25 mL of DMF, under argon at 0°C, was added 10.5 g (0.15 mol) of imidazole followed by 20.7 g (0.14 mol) of t-butyldimethylsilyl chloride. The reaction was slowly warmed to RT and stirred for 18 h at which time the reaction was diluted with ether and washed with NH_4Cl, water, Na_2CO_3, brine and dried ($MgSO_4$). The resulting colorless liquid 

, 50 g, contained approximately 15% of the disilylated compound.

To a solution of 8.5 g (42 mmol) of the above alcohol in 50 mL of THF, under argon at 0°C, was added 7.3 g (108 mmol) of imidazole and 16.7 g (64

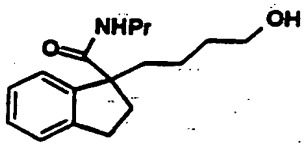
mmol) of triphenylphosphine. This mixture was stirred for 45 min (solution became homogeneous) at which time 16.2 g (64 mmol) of iodine in 50 mL of THF was added dropwise over 20 min. The reaction was stirred for 1 h, diluted with hexanes and washed with 1M sodium bisulfite, Na_2CO_3, brine and dried (Na_2SO_4). The resulting residue was triturated with ether (3x), filtered (to remove triphenylphosphine oxide) and evaporated to provided 10 g (61%) of title iodobutane as a pale yellow oil.

D.



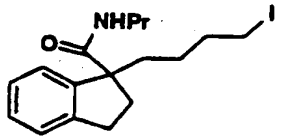
To a stirred solution of diisopropylamine (0.95 mL, 6.8 mmol) in 10 mL of THF at -5°C under argon was added n-butyllithium solution (2.70 mL, 6.75 mmol, 2.5 M in hexane) and stirred for 15 min. A solution of Part B compound (593 mg, 3.38 mmol) in 5 mL of THF was added over 10 min. The resulting deep orange solution was stirred for 30 min and a solution of Part C 1-t-butyldimethyl-silyloxy-4-iodobutane (1.03 g, 3.31 mmol) in 5 mL of THF was added. A light yellow solution forms within 1 hour. The reaction mixture was quenched with saturated sodium bicarbonate solution and extracted twice with ethyl acetate. The organic extracts were combined, dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel gave title compound as a colorless oil, 680 mg, 58%.

E.



To a solution of Part D compound (675 mg, 1.73 mmol) in 5 mL of THF at room temperature under argon was added a solution of tetrabutylammonium fluoride (3 mL, 3 mmol, 1 M in THF). After 1 h, the reaction mixture was partitioned between ethyl acetate and 10% citric acid solution. The organic extract was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (2.5 x 15 cm column, 1:4 hexanes/ethyl acetate) provided title compound as a colorless oil, 380 mg, 80%.

F.



To a solution of Part E compound (380 mg, 1.38 mmol) in 5 mL of THF under argon at room temperature was added triphenylphosphine (365 mg, 1.39 mmol) and imidazole (210 mg, 3.0 mmol) and then iodine (360 mg, 1.39 mmol) in 5 mL of THF. After 15 min, the reaction was quenched with 5% $NaHSO_3$ solution and extracted with ether. The organic extract was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, 5:7 ethyl acetate/hexanes) gave title compound as a colorless oil, 442 mg, 83%.

G. 2,3-Dihydro-1-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-1H-indene-1-carboxamide

To a stirred solution of Part F compound (430 mg, 1.12 mmol) in 5 mL of DMF at room temperature under argon was added Example 1 Part G compound (265 mg, 1.23 mmol). The reaction was heated to 50°C. After 14 h, the reaction was quenched with 10% $NaHSO_3$ solution and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$), evaporated and re-evaporated twice from toluene. Purification by flash chromatography on silica gel (2.5 x 15 cm column, 1:9 methanol/ethyl acetate) gave title compound as a colorless amorphous solid, 425 mg, 88%.

IR (thin film) 3470, 2940, 1680, 1660, 1530, 1510, 1470, 1455, 740 cm^{-1}.

Calculated for $C_{30}H_{39}N_3O_2 \cdot 0.94\ H_2O$:
C, 73.45; H, 8.30; N 8.57
Found: C, 73.44; H, 8.11; N 8.47.

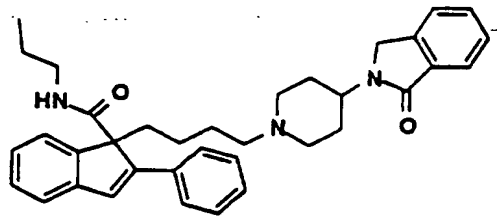
MS (electrospray, + ions) m/e 474 (M+H).

^1H NMR ($CDCl_3$, 300 MHz)

δ	7.83 (d, 1H, J = 7.3 Hz)
	7.52-7.44 (m, 3H)
	7.30-7.23 (m, 4H)
	5.53 (t, 1H, J = 5.5 Hz)
	4.35 (s, 2H)
	4.30 (5-plet, 1H, J = 5.3 Hz)
	4.01 (dd, 1H, J = 7.2, 7.8 Hz)
	3.13 (m, 2H)
	3.04 (d, 2H, J = 9.8 Hz)

2.92 (t, 2H, J = 6.7 Hz)
2.50 (5-plet, 1H, J = 5.5 Hz)
2.38 (t, 4H, J = 7.7 Hz)
2.18-1.84 (m, 9H)
1.56-1.35 (m, 6H)
0.81 (t, 3H, J = 7.4 Hz) ppm.

Example 27

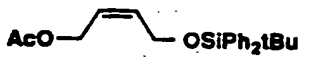


1-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-2-phenyl-N-propyl-1H-indene-1-carboxamide

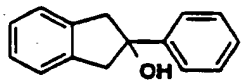
A. 

To a slurry of sodium hydride (6.975 g, 60% mineral oil dispersion, 0.174 mol) in 200 mL of THF at room temperature under argon was added 2-butene-1,4-diol (15.36 g, 0.174 mol) over 20 minutes. Gas evolved and a thick precipitate formed. The slurry was stirred for 16 h and then was rapidly treated with t-butyl diphenylchlorosilane (47.82 g, 0.174 mol). The reaction warms to 40°C autogenously and a clear solution formed. After 15 min, the reaction was quenched with water and extracted twice with hexanes. The organic layers were combined, dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (12 x 30 cm column,

dichloromethane) gave title compound as a colorless oil, 46.6 g, 82%.

B. 

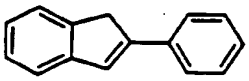
To a stirred solution of Part A compound (6.53 g, 20.0 mmol) and triethylamine (3.53 mL, 25.3 mmol) in 50 mL of dichloromethane at room temperature under argon was added acetic anhydride (2.4 mL, 22.5 mmol) and DMAP (20 mg, 0.16 mmol). The reaction was evaporated at less than 30°C and the residue partitioned between 10% citric acid and hexanes. The organic layer was washed with water and saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. The isolated colorless oil, (7.02 g, 95%), was used without further purification in Part F.

C. 

Anhydrous cerium chloride (16.00 g, 64.9 mmol) was stirred in an evacuated flask heated in an oil bath to 145°C for 2 h. The flask is flooded with argon, cooled to room temperature and then to 0°C in an ice bath. To this powder was added 150 mL of THF. The stirred slurry was warmed to room temperature. After 14 h, the flask was again cooled to 0°C and phenylmagnesium chloride solution (21.2 mL, 63.6 mmol, 3 M in ether) was added. The resulting yellow slurry was stirred for 1.5 h and then a solution of 2-indanone (5.45 g, 41.2 mmol, freshly chromatographed) was added. After 30 min, the reaction mixture was quenched with 10% citric acid

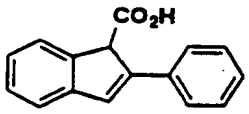
and extracted twice with ether. The organic extracts were dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5 x 20 cm column, 17:3 dichloromethane/hexanes) gave title compound as a colorless oil, 6.66 g, 77%.

D.



To neat Part C compound (6.40 g, 30.4 mmol) was added potassium bisulfate (6.4 g, 47 mmol). The mixture was stirred under argon and placed in an oil bath heated to 160°C for 20 min. The resulting solid mass was cooled, partitioned between dichloromethane and water. The organic layer was dried ($MgSO_4$) and evaporated to provide title compound (5.84 g, 100%) as a white solid, mp 163-164°C.

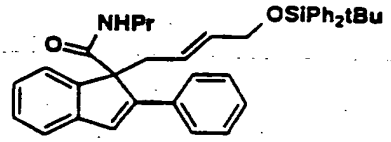
E.



To a solution of Part D compound (1.481 g, 7.70 mmol) in 20 mL of THF at 0°C under argon was added n-butyllithium (3.0 mL, 7.50 mmol, 2.5 M in hexanes) over 10 min. The resulting deep orange solution was stirred for 1h. The reaction was quenched with several small pieces of THF-washed dry ice. The resulting thick yellow slurry was stirred for 1 h and then treated with 20 mL of 2 M potassium hydroxide solution. This solution was extracted twice with ether and the aqueous residue was brought to pH 2 with 3 N sulfuric acid. The mixture was

extracted three times with ethyl acetate, the extracts combined, dried ($MgSO_4$) and evaporated to give title compound as a light yellow powder (1.50 g, 82%), mp 212-215°C.

F.



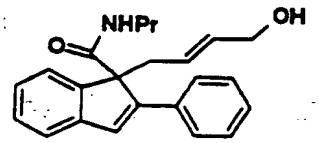
A mixture of Part E compound (890 mg, 3.77 mmol), Part B compound (2.55 g, 3.77 mmol) and triphenylphosphine (190 mg, 0.724 mmol) was evaporated twice from toluene. The mixture was dissolved in 20 mL of THF, stirred under argon and treated with bis(trimethylsilyl)acetamide (BSA) (3.7 mL, 15 mmol). After 30 min, tetrakis(triphenylphosphine)palladium(0) (430 mg, 0.39 mmol) was added and the reaction set to reflux. After 16h, the orange solution was cooled, evaporated and re-evaporated twice from methanol. The gummy residue was dissolved in ether and washed once with 10% citric acid. The organic extract was dried ($MgSO_4$), evaporated and re-evaporated once from toluene.

To a stirred solution of this product in 10 mL of dichloromethane under argon at room temperature was added oxalyl chloride (0.9 mL, 7.0 mmol) and then DMF (0.05 mL). After 1 h, the reaction was evaporated to give an orange oil which was dissolved in 10 mL of THF.

This solution was added to a stirred solution of n-propylamine (1.4 mmol, 16 mmol) in 10 mL of THF at 0°C over 10 min. After 1h, the reaction mixture was diluted with ether and washed once with 10%

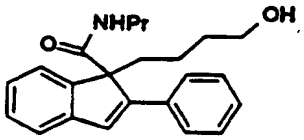
citric acid. The organic extract was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5 x 20 cm column, dichloromethane) gave title compound as an orange oil, 1.50 g, 77%.

G.



To a stirred solution of Part F compound (2.15 g, 4.18 mmol) in 15 mL of THF at room temperature under argon was added tetrabutylammonium fluoride (10 mL, 10 mmol, 1 M in THF). After 1h, the reaction was quenched with brine and extracted three times with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, 3:2 hexanes/ethyl acetate) gave title compound as a colorless glass, 1.09 g, 75%.

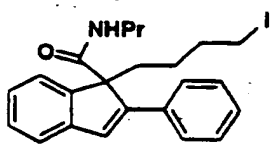
H.



To a solution of Part G compound (209 mg, 0.60 mmol) in 10 mL of ethanol at room temperature purged with argon was added 5% Pd-C (45 mg). The flask is evacuated and purged with argon twice and with hydrogen from a baloon and stirred under a hydrogen atmosphere for 30 min. The reaction was filtered through Celite and the filtrate evaporated. Purification by flash chromatography (2.5 x 15 cm

column, 1:1 hexanes/ethyl acetate) gave title compound as a white foam, 92 mg, 44%.

I.



To a stirred solution of Part H compound (90 mg, 0.26 mmol) in 2 mL of THF at room temperature under argon was added triphenylphosphine (68 mg, 0.26 mmol) and imidazole (40 mg, 0.57 mmol) and then iodine (65 mg, 0.26 mmol) in 2 mL of THF. After 10 min, the reaction was quenched with 10% $NaHSO_3$ solution and extracted with ether. The organic extract was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (2.5 x 15 cm column, dichloromethane) gave title compound as a white solid, 87 mg, 73%, mp 125-127°C.

J. 1-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-2-phenyl-N-propyl-1H-indene-1-carboxamide

To a stirred solution of Part I compound (74 mg, 0.161 mmol) in 2 mL of DMF at room temperature under argon was added Example 1 Part G compound (40 mg, 0.181 mmol). The reaction was heated to 50°C. After 14 h, the reaction was quenched with 10% $NaHSO_3$ solution and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$), evaporated and re-evaporated twice from toluene. Purification by flash chromatography on silica gel (2.5 x 15 cm column, 1:12 methanol/ethylacetate) gave title compound as a white solid, 80 mg, 91%, mp 156-57°C.

IR (KBr pellet) 3326, 2942, 2863, 1678, 1622, 1512, 1454, 1302, 737 cm^{-1}.

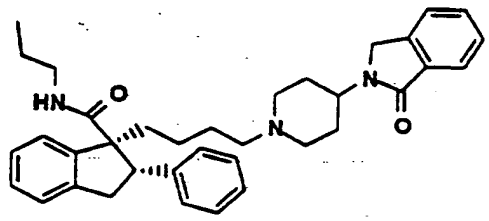
MICROANALYSIS Calculated for $C_{36}H_{41}N_3O_2 \cdot 1.17\ H_2O$:
C, 76.02; H, 7.68; N 7.39
Found: C, 76.02; H, 7.43; N 7.30.

MS (electrospray, + ions) m/e 548 (M+H).

^1H NMR ($CDCl_3$, 300 MHz)

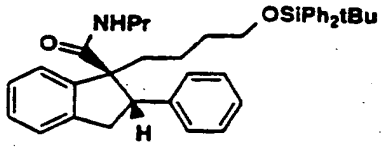
δ	7.83 (d, 1H, J = 7.6 Hz)
	7.56 (d, 2H, J = 7.6 Hz)
	7.40 (s, 1H)
	7.54-7.2 (m, 9H)
	5.32 (t, 1H, J = 5.8 Hz)
	4.30 (d, 1H, J = 7.3 Hz)
	3.05 (m, 2H)
	2.85 (d, 2H)
	2.62 (dt, 1H, J = 4.2, 9.2 Hz)
	2.31 (dt, 1H, J = 4.5, 9.2 Hz)
	2.06 (m, 2H)
	1.94 (m, 2H)
	1.71 (m, 4H)
	1.26 (m, 4H)
	0.59 (t, 3H, J = 7.3 Hz)
	0.6 (m, 1H)
	0.43 (m, 1H) ppm.

Example 28



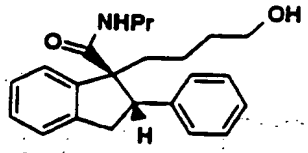
trans-2,3-Dihydro-1-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-2-phenyl-N-propyl-1H-indene-1-carboxamide

A.



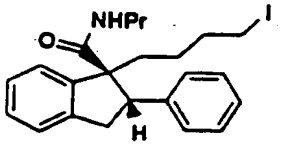
To a solution of 682 mg (1.34 mmol) of compound Example 27 Part F in 10 mL of ethanol at room temperature was added 2 g (32 mmol) of ammonium formate. The slurry was stirred and purged with nitrogen for 20 min. After adding 10% palladium-on-carbon (1 g), the reaction was stirred under argon for 16 h. The reaction mixture was filtered through Celite®, washing with ethyl acetate. The filtrate was washed twice with water and once with brine, dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, 1:99 ether/dichloromethane) gave title compound as a colorless oil, 354 mg, 52%.

B.



To a stirred solution of Part A compound (315 mg, 0.534 mmol) in 3 mL of THF at room temperature under argon was added tetrabutylammonium fluoride (1.0 mL, 1.0 mmol, 1 M in THF). After 1h, the reaction was quenched with brine and extracted three times with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated. Purification by flash chromatography (2.5 x 15 cm column, 3:5 hexanes/ethyl acetate) gave title compound as a white foam, 135 mg, 72%.

C.



To a stirred solution of Part B compound (127 mg, 0.361 mmol) in 2 mL of THF at room temperature under argon was added triphenylphosphine (95 mg, 0.36 mmol) and imidazole (60 mg, 0.86 mmol) and then iodine (92 mg, 0.36 mmol) in 1 mL of THF. After 15 min, the reaction was quenched with 5% $NaHSO_3$ solution and extracted with ether. The organic extract was dried ($MgSO_4$) and evaporated. Purification by flash chromatography (2.5 x 15 cm column, dichloromethane) gave title compound as a colorless glass, 101 mg, 61%.

D. trans-2,3-Dihydro-1-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-butyl]-2-phenyl-N-propyl-1H-indene-1-carboxamide

To a stirred solution of Part C compound (100 mg, 0.217 mmol) in 3 mL of DMF at room temperature under argon was added Example 1 Part G compound (54 mg, 0.244 mmol). The reaction was heated to 50 °C. After 14 h, the reaction was quenched with 10% $NaHSO_3$ solution and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$), evaporated and re-evaporated twice from toluene. Purification by flash chromatography on silica gel (2.5 x 15 cm column, 1:9 hexane/ethyl-acetate) gave title compound as a light yellow amorphous glass, 105 mg, 88%.

IR (KBr pellet) 3432, 2934, 2872, 1676, 1516, 1470, 1454, 766, 737 cm^{-1}.

MICROANALYSIS Calculated for $C_{36}H_{43}N_3O_2 \cdot 1.54\ H_2O$:
C, 74.87; H, 8.04; N 7.64
Found: C, 74.88; H, 7.82; N 7.33.

MS (electrospray, + ions) m/e 550.5 (M+H).

^1H NMR ($CDCl_3$, 300 MHz)

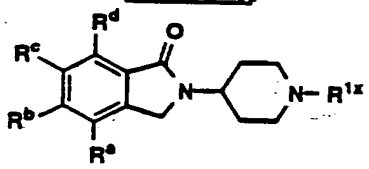
δ	7.82 (d, 1H, J = 7.3 Hz)
	7.51-7.14 (m, 12H)
	5.66 (t, 1H, J = 5.2 Hz)
	4.33 (m, 2H)
	4.26 (dd, 1H, J = 0.7, 3.6 Hz)
	4.01 (dd, 1H, J = 7.2, 7.8 Hz)
	3.28 (m, 4H)
	2.95 (d, 2H, J = 10.7 Hz)

2.24 (m, 2H)
2.12 (t, 2H, J = 11.1 Hz)
1.80 (m, 4H)
1.53-1.16 (m, 8H)
0.88 (t, 3H, J = 7.3 Hz) ppm.

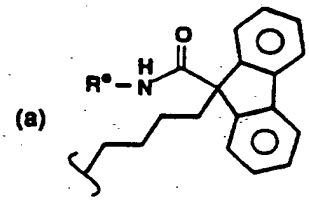
Additional compounds falling within the scope of the present invention are described by the following structures. Substituents for each example are identified in the table following each structure.

Examples

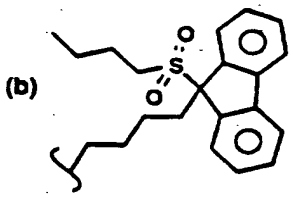
Table A



where R^{1x} is

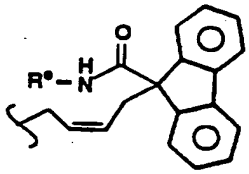


(a) (R^e=C_3H_7 or CF_3CH_2)



(b)

or (c)



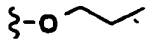
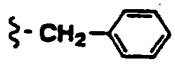
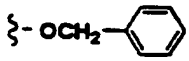
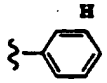
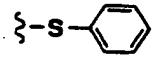
R^a	R^b	R^c	R^d
H	H	H	F
H	H	H	
H	H	F	Cl
H	H	CF_3	H
H	OCH_3	H	H
H	H	H	
	H		H
H	H		H
F	Cl	H	H
H	H	H	

Table A (continued)

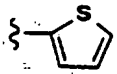
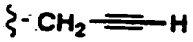
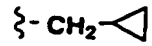
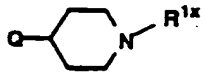
R^a	R^b	R^c	R^d
H	H	Cl	H
H	H	H	
H	H	H	H
H	H	H	Cl
H	H	CH_3	H
H	CH_3	H	
SCH_3	H	H	H
H	H	OCH_3 H	
H	H	H	SCH_3
H	H	H	H
H	H	H	
H		H	
H	H	H	H
H	H	H	

Table B



where R^{1x} is (a), (b) or (c) as in Table A

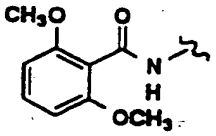
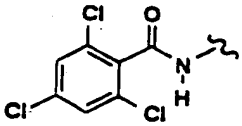
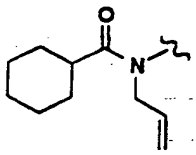
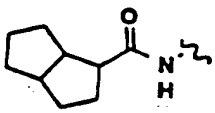
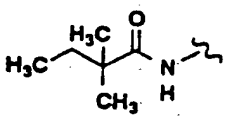
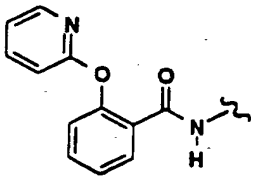
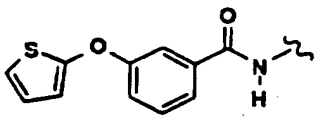
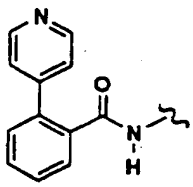
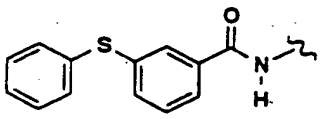
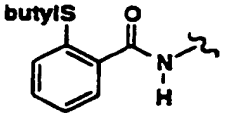
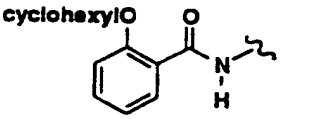
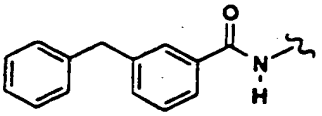
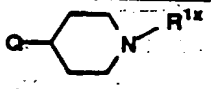
Examples of Q













Table B (continued)



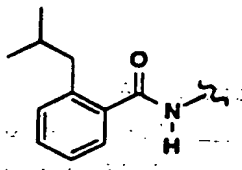
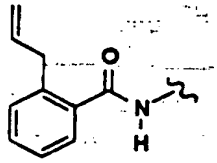
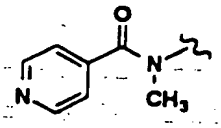
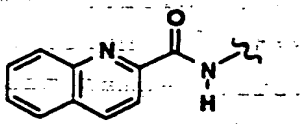
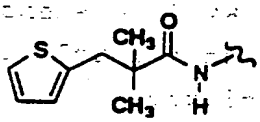
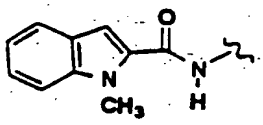
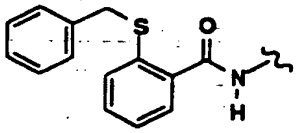
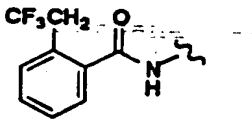
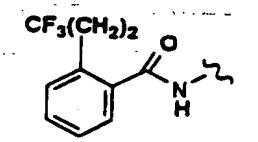
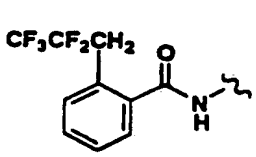
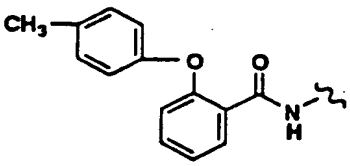
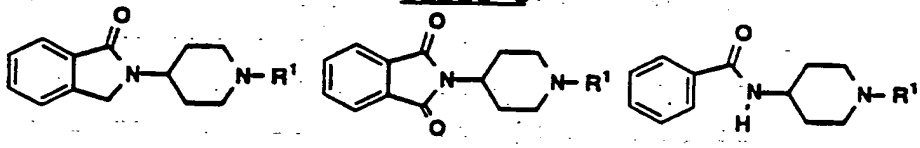
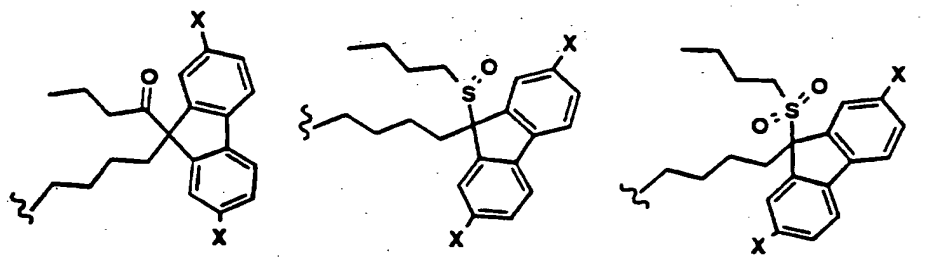
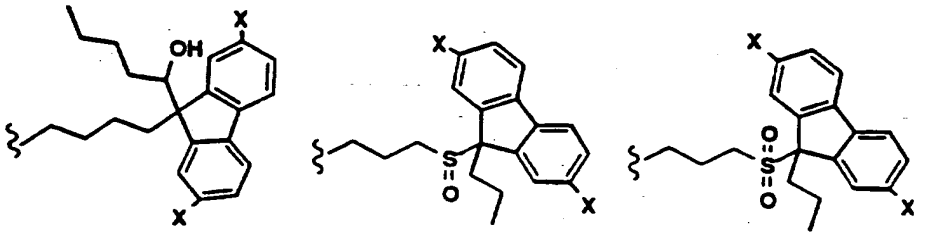
Examples of Q
  
  
  
 

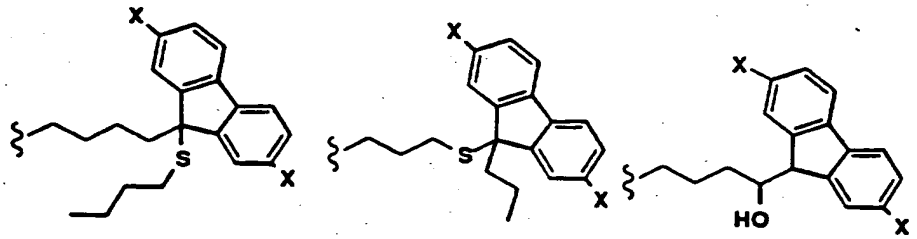
Table C

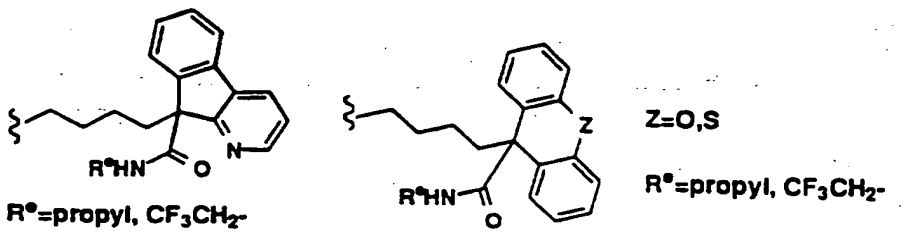


Examples of R^1









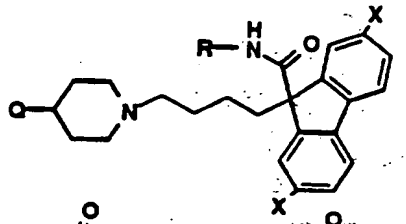
R*=propyl, CF_3CH_2-

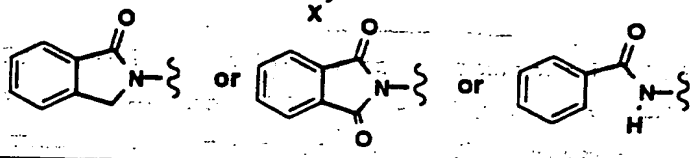
Z=O,S

R*=propyl, CF_3CH_2-

X for Table C = H or F

Table D



Q=  or or

X = H or F

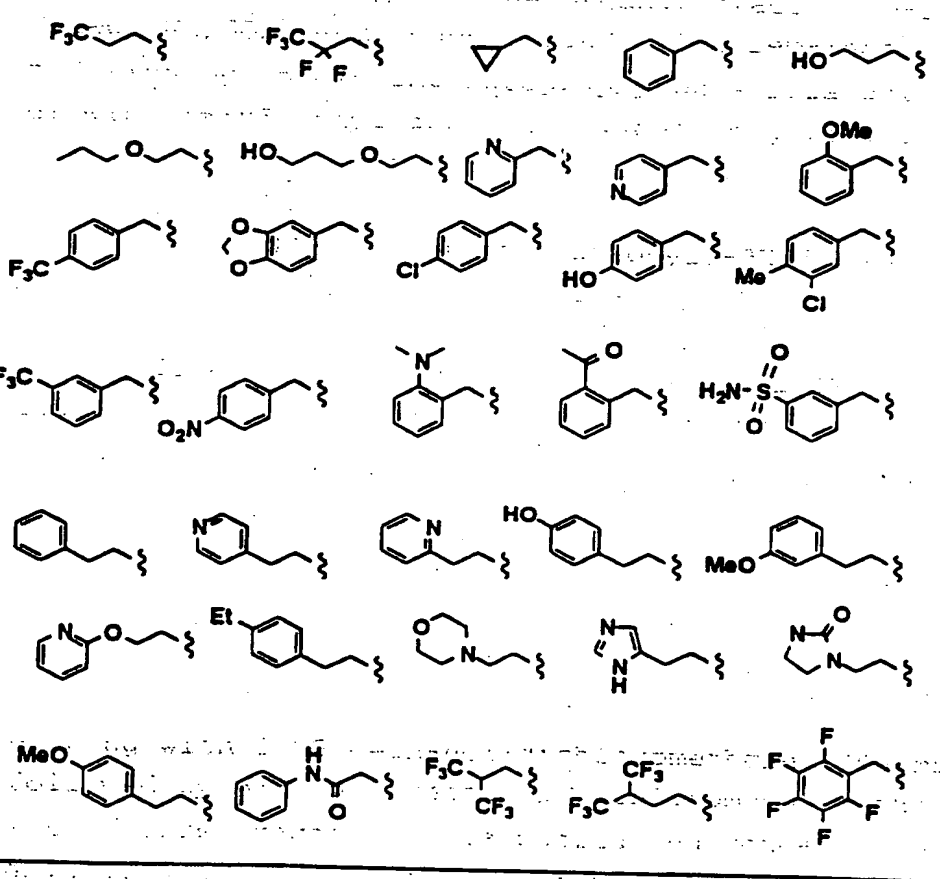
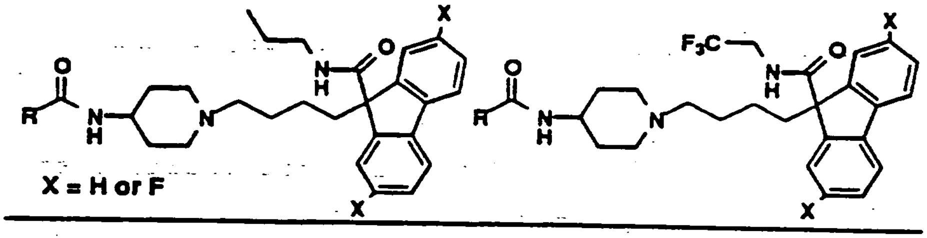
Example of R


Table E



Example of R

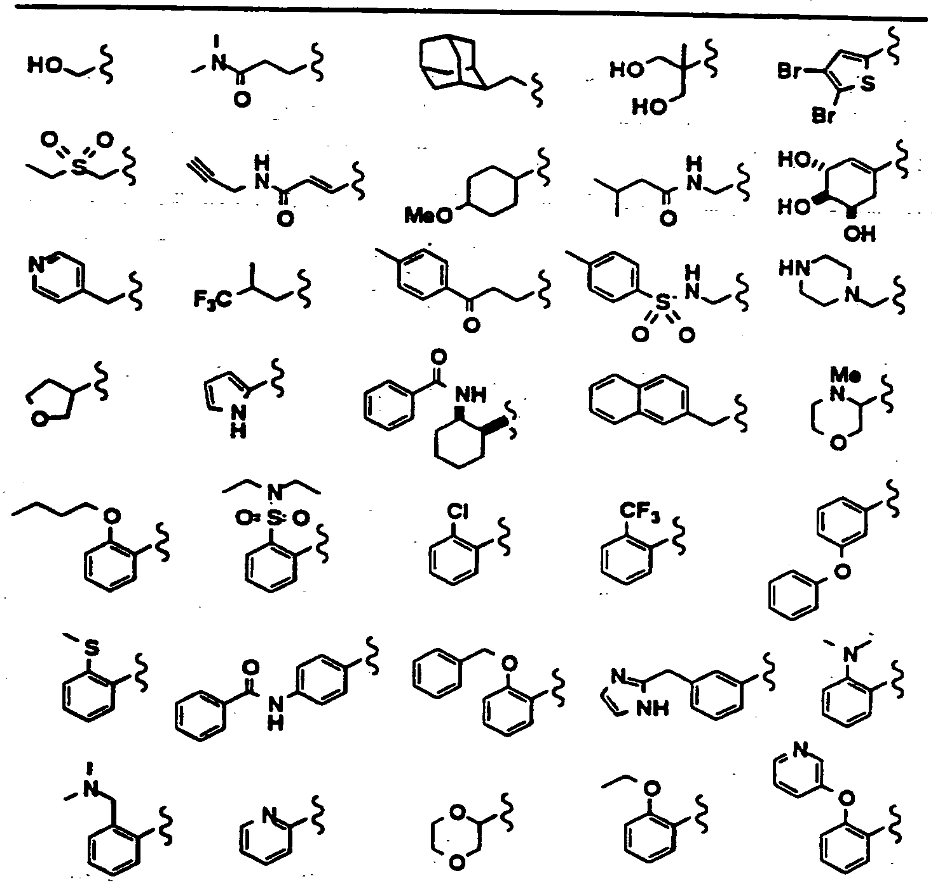


Table E (Cont'd)

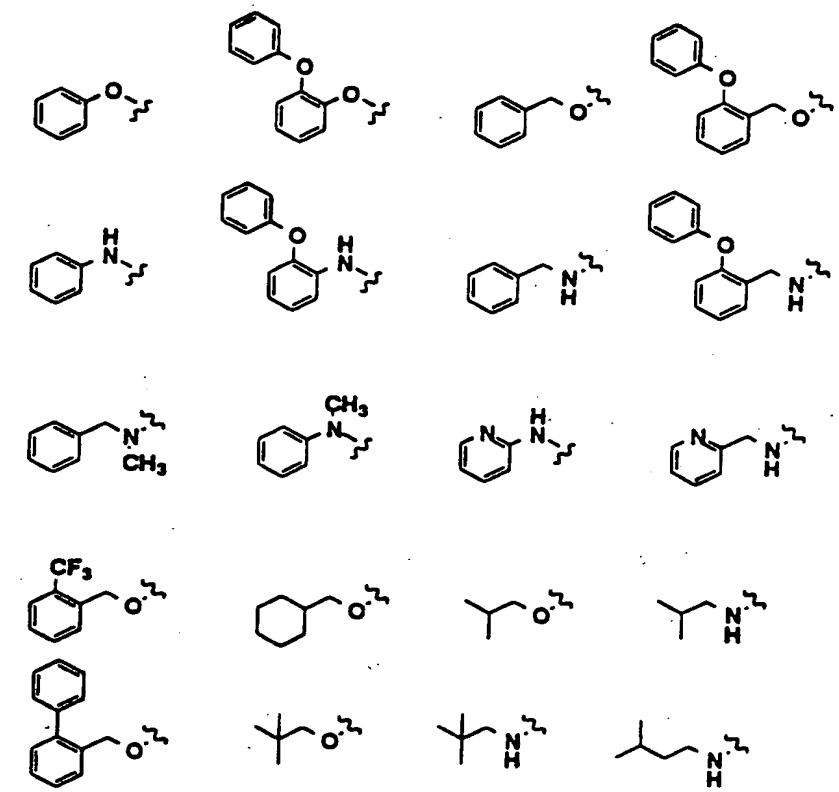
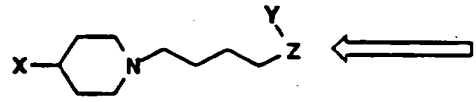
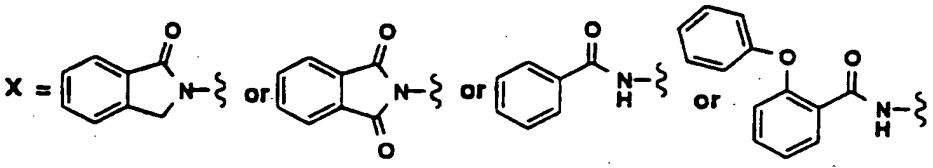
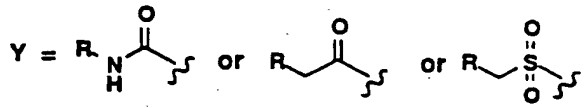


Table F



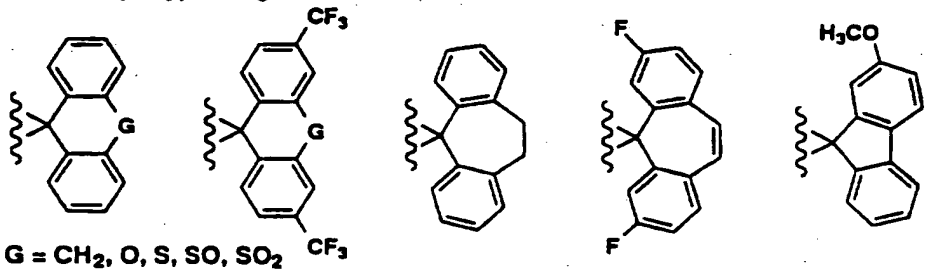
Fluorenyl-Type Compounds



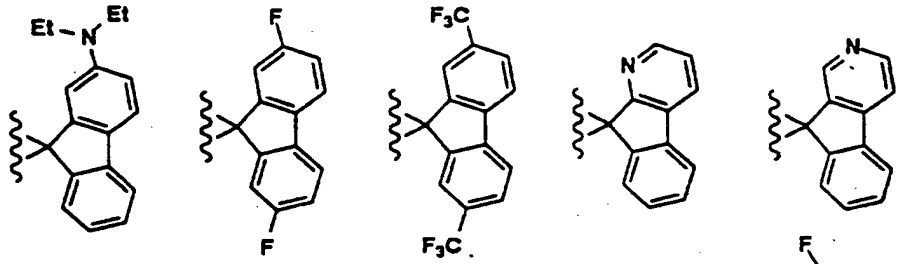


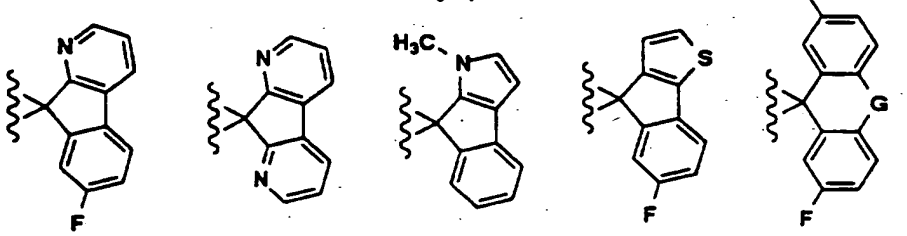
R = propyl or CF_3CH_2

Fluorenyl-Type Rings: Z =



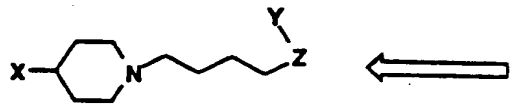
G = CH_2, O, S, SO, SO_2



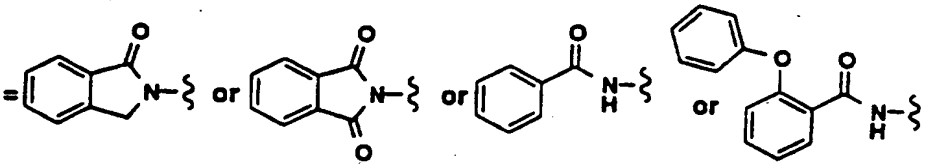


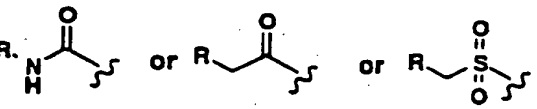
G = CH_2, O, S, SO, SO_2

Table G



Indenyl-Type Compounds

X =  or or or

Y =  or or R = propyl or CF_3CH_2

Indenyl-Type Rings: Z =

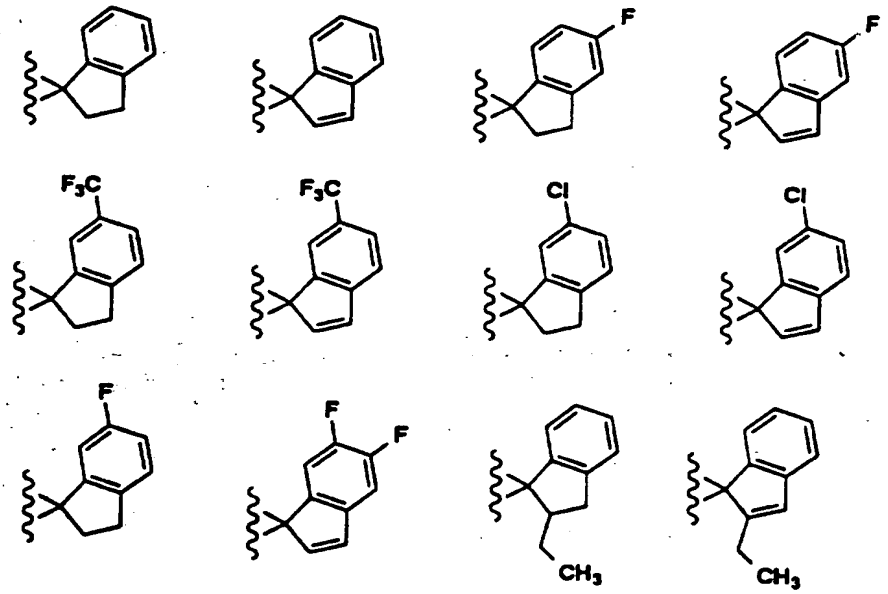


Table G (cont'd)

Indenyl-Type Rings: Z =

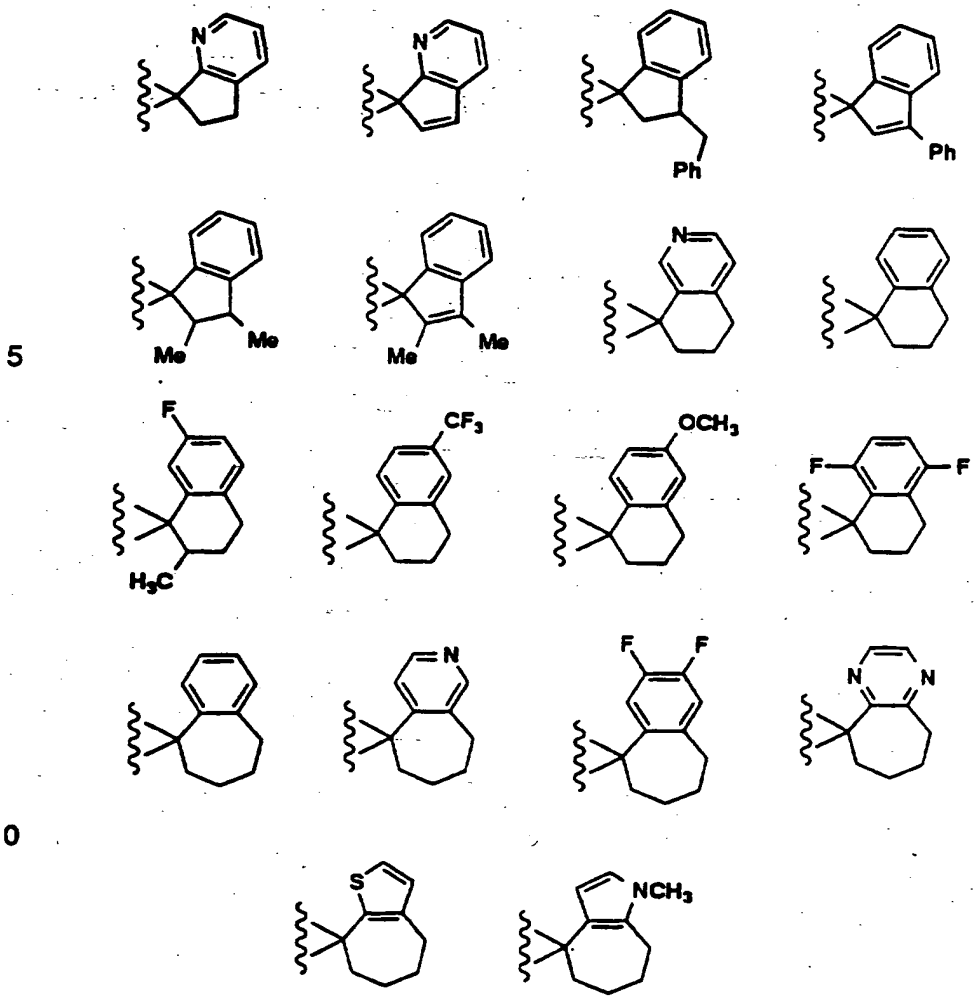
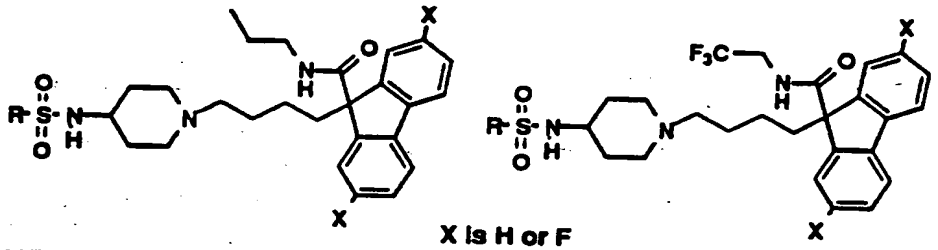
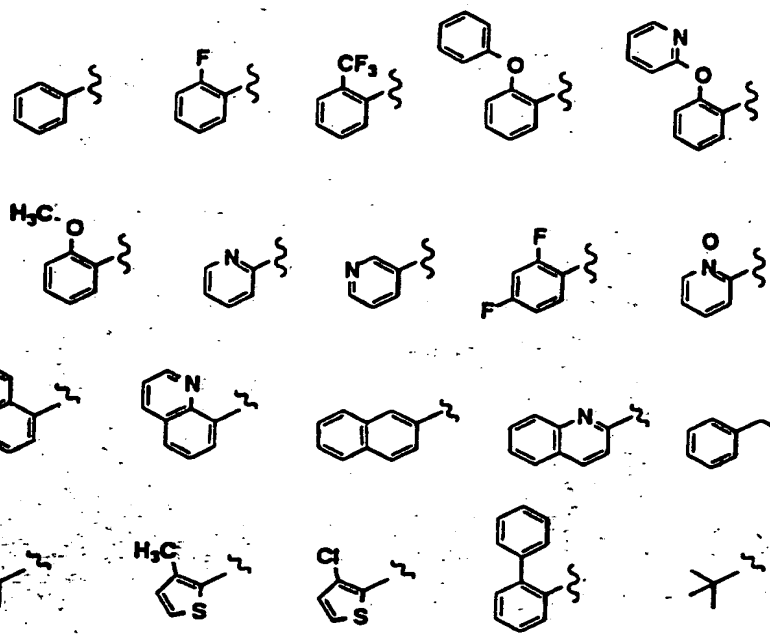


Table H



X is H or F

Example of R


In the foregoing Tables which set out compounds of the invention of formulae I and II, that is compounds which include the 4-substituted piperidine isomers, it will be understood that the formulae I and II compounds may be substituted with compounds of the invention of formulae Ii and IIi, that is compounds which include the 3-substituted piperidine isomers.

Example 29

cis-9-[4-[4-(2,3-Dihydro-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide, N-oxide

A slurry of 3-chloroperoxybenzoic acid (approx. 50%) (341 mg, 0.99 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of Example 1 compound (524 mg, 0.99 mmol) in CH_2Cl_2 (1 mL) at 0°C under argon. The reaction was stirred at 0°C for 20 min, diluted with CH_2Cl_2 (15 mL), washed with saturated $NaHCO_3$ (5 mL) and brine (5 mL), then dried over $MgSO_4$. Evaporation gave 612 mg of a white foam, which was purified by flash chromatography on silica gel (75 g) eluting with a step gradient of 4% to 5% to 7% to 10% MeOH/CH_2Cl_2 to give title compound (308 mg, 58%) as a white foam.

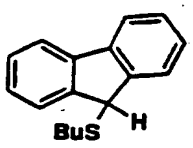
MS (ES): 538 [M+H]

Anal. Calcd. for $C_{34}H_{39}N_3O_3 \cdot 1.5\ H_2O$:
C, 72.29; H, 7.50; N, 7.44
Found: C, 72.32; H, 7.28; N, 7.41.

Example 30

2-[1-[4-[9-(Butylsulfonyl)-9H-fluoren-9-yl]butyl]-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one

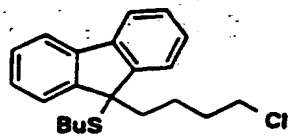
A.



A solution of 9-hydroxy-(9H)-flourene (1.58 g, 10.0 mmol) and butanethiol (0.72 g, 8.00 mmol) in 10 mL of dichloromethane at -20°C was treated with borontrifluoride etherate (1.28 g, 9.00 mmol). The reaction was stirred for 1 h at -20°C and warmed to room temperature. After stirring for 18 h the contents of the flask were purified by column chromatography on silica gel (100 g) with hexanes followed by 1:9 dichloromethane/hexanes to give 1.54 g (75%) of title compound as a colorless oil.

TLC Silica gel (1:9 dichloromethane/hexanes) R_f= 0.5.

B.

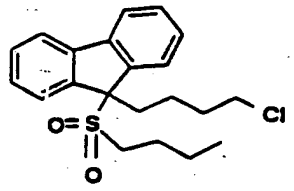


A solution of Part A compound (1.0 g, 3.93 mmol) in 10 mL of THF at -78°C was treated with n-butyllithium in hexanes (1.75 mL, 4.40 mmol) followed by 1-chloro-4-bromo-butane (0.81 g, 4.70 mmol). The reaction was stirred for 0.5 h and warmed to room temperature for 18 h. The contents of the flask were diluted with 30 mL of aqueous NH_4Cl solution and 30

mL of ethyl acetate. The organic fraction was dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with 2:98 acetone/dichloromethane (500 mL) followed by 15:85 dichloromethane/hexanes to give 1.00 (73%) of title compound as a colorless oil.

TLC Silica gel (2:8 dichloromethane/hexanes) R_f= 0.4.
Mass Spec. (ES, + ions) m/e 255 (M-SC_4H_9).

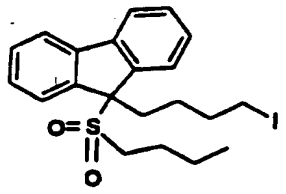
C.



To a solution of Part B compound (0.30 g, 0.86 mmol) in dichloromethane (5 mL) at 0°C was added 3-chloroperoxybenzoic acid (m-CPBA) (0.37 g, 80% by weight = 0.1.72 mmol) in one portion. The mixture was stirred for 1 h when it was diluted with 0.1 M K_2CO_3 (20 mL) and ether (30 mL). The organic fraction was dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with 15:85 ethyl acetate/hexanes to give 0.24 g (75%) of title compound as a colorless oil.

TLC Silica gel (2:8 dichloromethane/hexanes) R_f= 0.07.

D.



To a solution of Part C compound (0.24 g, 0.64 mmol) in 2-butanone (10 mL) at RT was added NaI (1.00 g, 6.66 mmol) in one portion. The mixture was refluxed for 30 h when it was diluted with water (20 mL) and ether (30 mL). The organic fraction was dried (Na_2SO_4) and concentrated. The remainder was purified by column chromatography on silica gel (50 g) with 15:85 ethyl acetate/hexanes to give 0.24 g (81%) of title compound as a colorless oil.

E. 2-[1-[4-[9-(Butylsulfonyl)-9H-fluoren-9-yl]butyl]-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one

To a stirred solution of 0.70 g (1.49 mmol) of Part D compound in 6 mL of DMF at RT was added 0.38 g (1.80 mmol) of Example 1 Part G compound. The reaction mixture was warmed to 55°C and allowed to stir for 24 h. The mixture was diluted with $NaHCO_3$ solution (50 mL) and ethyl acetate (50 mL). The layers were separated, the organics dried (Na_2SO_4) and concentrated. The remainder was purified by flash column chromatography on silica gel (100 g) eluting with 5:95 methanol/dichloromethane (700 mL) followed by 5:95:0.5 methanol/dichloromethane/NH_3 (1L). Pure fractions were pooled and concentrated to give 0.70 g (85%) of title compound as a thick oil which solidified after standing.

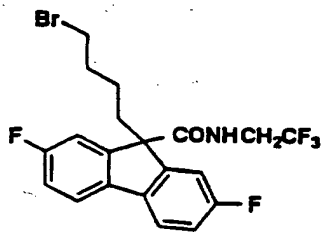
mp: 130-132°C.
TLC Silica gel (5:95:1 methanol/dichloromethane/NH_3)
R_f= 0.35.

Anal. Calcd. for $C_{34}H_{40}N_2SO_3$ + 0.5 H_2O:
C, 72.79; H, 7.30; N, 4.96; S, 5.68
Found: C, 72.25; H, 7.15; N, 5.00; S, 5.69.

Example 31

9-[4-[[4-[(1,1-Dimethylethoxy)carbonyl]amino]-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A.



A Solution of Example 3 Part B compound (8.00 g, 32.5 mmol) in 100 mL of THF at room temperature was carefully evacuated and then purged with argon four times. The stirred solution was cooled to -25°C and a solution of n-butyllithium (26.5 mL, 2.5 M in hexanes, 66.3 mmol) was added over 15 min. The resulting slurry was stirred for 1 h and cooled to -78°C. Neat dibromobutane (6.0 mL, 50.0 mmol) was added in one portion and the reaction was allowed to warm to room temperature over the course of 6 h. After an additional 14 h, the reaction mixture was poured into 1 M hydrochloric acid (70 mL) and extracted twice with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and evaporated.

The semi-solid residue was triturated with hexanes and filtered to give 11.32 g of an off-white solid.

To a slurry of the above solid (11.0 g) in 25 mL of dichloromethane at room temperature under argon was added a solution of oxalyl chloride (25 mL, 2.0 M in dichloromethane, 50 mmol) followed by 0.5 mL (6.0 mmol) of DMF. After 1 h, the reaction was evaporated at less than 25°C and the residue redissolved in 30 mL of THF. This solution was added over 20 min to a solution of 2,2,2-trifluoroethyl amine (6.10 g, 61.5 mmol) in 25 mL of THF at -10 °C under argon. After 2 h, the reaction was quenched with 10% citric acid solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. Purfication by flash chromatography (12 x 20 cm column, 7:3 dichloromethane/hexanes as elutant) on silica gel provided title compound as a white solid, 9.03 g, 60% yield from Example 3 Part B compound, mp 147-148°C.

B. 9-[4-[[4-[(1,1-Dimethylethoxy)carbonyl]-amino]-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

To a stirred solution of Part A compound (5.48 g, 11.9 mmol) in 20 mL of DMF at room temperature under argon was added Example 10 Part B compound (2.85 g, 14.2 mmol). The reaction was heated to 50°C. After 14 h, the reaction was quenched with 10% $NaHSO_3$ solution and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$), evaporated and re-evaporated twice from toluene. Purification by flash chromatography on silica gel (2.5 x 15 cm column, ethyl acetate elutant) gave title compound, as a white solid, 6.23 g, 90%, mp 152-154°C.

Example 32

9-[4-[4-[(2-Phenoxybenzoyl)amino]-1-piperidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

Following the procedure in Example 12 Part B, 2-phenoxybenzoic acid (2.0 g, 9.34 mmol) was transformed into the acid chloride then reacted with Example 36 Part D compound (4.84 g, 9.34 mmol) to give a white solid (5.0 g). The product was dissolved in MeOH (5 mL), then 0.77M HCl in ethyl ether (15 mL) was added. The solution was evaporated and heated in a vacuum oven (55°C) overnight to give title compound (5.1 g, 82%) as a white solid.

m.p. 123-127°C.
MS (ES, + ion): 656 (M+H).

Anal. Calc. for $C_{38}H_{39}ClF_3N_3O_2 \cdot 0.7\ H_2O$:
C, 66.07; H, 5.90; N, 6.08; F, 8.25
Found: C, 66.05; H, 5.97; N, 5.96; F, 8.21.

Example 33

9-[4-[[4-(Benzoylamino)-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A solution of Example 31 compound (2.07 g, 3.56 mmol) in 10 mL of 4 N hydrogen chloride in dioxane was stirred, protected by a calcium chloride drying tube, for 3 h. The solution was evaporated at 30°C and the resulting solid was re-dissolved in 20 mL of THF. To this stirred solution, cooled to -10°C under argon, was added triethylamine (1.24 mL, 8.9 mmol) and then benzoyl chloride (0.46 mmol, 4.0 mmol) over 10 min. After 1 h, the reaction was quenched with saturated sodium bicarbonate solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. Purfication by flash chromatography on silica gel (5 x 20 cm column, 1:19 methanol/ethylacetate as elutant) provided, after recrystallization from ethyl acetate/hexanes, title compound as a white solid, 1.83 g, 87% yield, mp 177-179°C.

Anal. Calc'd for $C_{32}H_{32}F_5N_3O_2 \cdot 0.25\ H_2O$:
C, 65.13; H, 5.55; F, 16.10; N, 7.12
Found: C, 65.10; H, 5.49; F, 15.85; N, 7.12.

MA (electrospray, + ions) m/e 586 (M+H).

Example 34

9-[4-[[4-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A solution of Example 31 compound (2.02 g, 3.47 mmol) in 10 mL of 4 N hydrogen chloride in dioxane was stirred, protected by a calcium chloride drying tube, for 3 h. The solution was evaporated at 30 °C and partitioned between saturated sodium bicarbonate solution and dichloromethane. The organic layer was separated, dried (Na_2SO_4) and evaporated to give a white solid. To this residue was added 550 mg (3.71 mmol) of phthalic anhydride under an argon atmosphere. The solids were melted together at 150°C for 6 h. On cooling, the resulting solid was recrystallized from ethyl acetate/hexanes to give title compound as a white solid, 1.71 g, 80% yield, mp 186-188°C.

Anal. Calc'd for $C_{38}H_{36}F_5N_3O_3 \cdot 0.13\ H_2O$:
C, 64.56; H, 4.94; N 6.87
Found: C, 64.56; H, 5.03; N 6.81.

MS (electrospray, + ions) m/e 612.2 (M+H).

Example 35

2,7-Difluoro-9-[4-[[4-[(2-phenoxybenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

To a solution of 565 mg (2.64 mmol) of 2-phenoxybenzoic acid (Aldrich) in 10 mL of dichloromethane under argon, was added 2 mL of oxalyl

chloride (2.0 M in dichloromethane, 4.0 mmol) and then 0.1 mL of DMF. After 1 h, the reaction was evaporated and the residue, 2-phenoxybenzoyl chloride, was redissolved in 10 mL of THF.

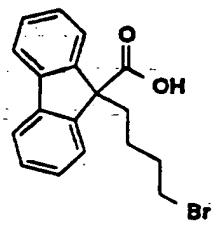
A solution of Example 31 compound (1.00 g, 1.76 mmol) in 10 mL of 4 N hydrogen chloride in dioxane was stirred, protected by a calcium chloride drying tube, for 3 h. The solution was evaporated at 30°C and the resulting solid was re-dissolved in 10 mL of THF. To this stirred solution, cooled to -10°C under argon was added triethylamine (0.95 mL, 6.5 mmol) and then the 2-phenoxybenzoyl chloride solution prepared above over 10 min. After 1 h, the reaction was quenched with saturated sodium bicarbonate solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. Purfication by flash chromatography on silica gel (5 x 20 cm column, 1:19 methanol/ethylacetate as elutant) provided, after recrystallization from ethyl acetate/hexanes, title compound as a white solid, 1.01 g, 85% yield, mp 168-69°C.

Anal. Calc'd for $C_{38}H_{36}F_5N_3O_3$:
C, 67.35; H, 5.35; F, 14.02; N 6.20
Found: C, 67.20; H, 5.35; F, 14.33; N 6.08.
MS (electrospray, - ions) m/e 676.3 (M-H).

Example 36

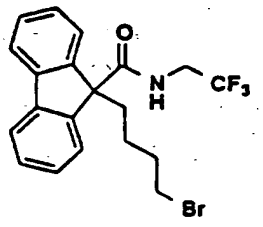
9-[4-[4-(Benzoylamino)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

A.



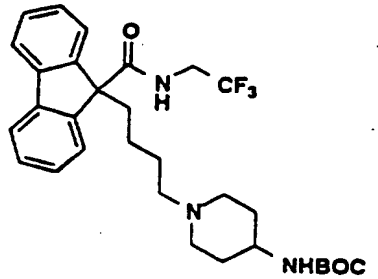
To a solution of 9-fluorenecarboxylic acid (50 g, 240 mmol) in THF (1200 mL) at 0°C was added dropwise a solution of n-butyllithium (2.5M, 211 mL, 530 mmol) in THF. The yellow reaction was stirred at 0°C for 1 h, then 1,4-dibromobutane (31.3 mL, 260 mmol) was added dropwise over 30 min. The reaction was stirred at 0°C for 30 min, then the reaction was warmed to RT for 30 h. The reaction was extracted with water (3 x 750 mL). The combined aqueous layers were extracted with ethyl ether (800 mL). The aqueous layer was made acidic with HCl solution (1N, 500 mL), then extracted with dichloromethane (3 x 750 mL). The combined organic layers were dried over $MgSO_4$. Evaporation gave title compound (71 g, 85%) as a white solid.

B.



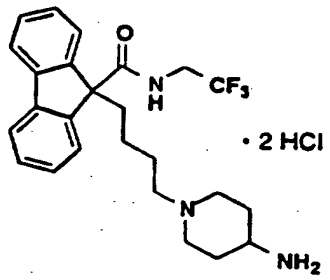
To a solution of Part A acid (60 g, 173 mmol) and DMF (100 µL) in CH_2Cl_2 (600 mL) under argon at 0°C was added oxalyl chloride (104 mL, 2.0M in CH_2Cl_2, 208 mmol) dropwise. The reaction was stirred at 0°C for 10 min, then warmed to RT and stirred for 1.5 h. The reaction was concentrated in vacuo to give the crude acid chloride as a yellow oil. To a suspension of 2,2,2-trifluoroethylamine hydrochloride (25.9 g, 191 mmol) in CH_2Cl_2 (500 mL) at 0°C under argon was added triethylamine (73 mL, 521 mmol) followed by dropwise addition of a solution of the crude acid chloride in CH_2Cl_2 (15 mL). The reaction was stirred at 0°C for 1 h, diluted with CH_2Cl_2 (500 mL), and washed with water (2 x 300 mL), 1N HCl (2 x 300 mL), saturated $NaHCO_3$ (2 x 300 mL), and brine (2 x 300 mL), then dried over $MgSO_4$. Evaporation gave 80 g of a oil which was purified by flash chromatography on silica gel (2.5 kg). The crude product was loaded in a mixture of CH_2Cl_2 and hexane, and eluted with a step gradient of 10% EtOAc/hexane (4L) to 15% EtOAc/hexane (2L) to 20% EtOAc/hexane (4L). Pure fractions were combined and evaporated to give title compound (52.5 g, 71%) as a white solid (mp 88-92°C).

C.



A mixture of Part B compound (29.5 g, 69.2 mmol), Example 10 Part B compound (14.5 g, 72.7 mmol), and anhydrous potassium carbonate (11.5 g, 83.0 mmol) in DMF (100 mL) was stirred at 50°C for 48 h, concentrated to dryness, and taken up in CH_2Cl_2 (500 mL). The solution was washed with saturated $NaHCO_3$ (3 x 80 mL) and brine (2 x 80 mL), then dried over $MgSO_4$. Evaporation gave a yellow oil which was purified by flash chromatography on silica gel (600 g), loaded in CH_2Cl_2, and eluted with a step gradient of 2% MeOH/CH_2Cl_2 (3L) to 3% MeOH/CH_2Cl_2 (4L). Pure fractions were combined and evaporated to give title compound (30 g, 86%) as a white foamy gum.

D.



To a solution of Part C compound (30.5 g, 60.4 mmol) in dioxane (120 mL) was added 4N HCl in dioxane (121 mL, 483 mmol). The reaction was stirred at RT for 4 h, then concentrated in vacuo to provide title compound (30 g) as a white foamy solid, containing a residual amount of dioxane.

E. 9-[4-[4-(Benzoylamino)-1-piperidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

To a solution of Part D compound (1.6 g, 3.08 mmol) and triethylamine (1.5 mL, 10.8 mmol) in dichloromethane (10 mL) at 0°C was added dropwise benzoyl chloride (0.4 mL, 3.40 mmol). The reaction was stirred at 0°C for 30 min. Dichloromethane (200 mL) was added and the solution was washed with water (2 x 50 mL), brine (2 x 50 mL) and dried over $MgSO_4$. Purification was performed by flash chromatography on silica gel (100 g), loaded and eluted with 2.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give a white solid. The product was dissolved in methanol (5 mL) and a solution of HCl in ethyl ether (0.77N, 5.19 mL) was added. The reaction was stirred at RT for 10 min, then evaporated to dryness. After drying in a vacuum oven (65°C, 72 h), title compound was obtained (1.3 g, 72%) as a white solid.

m.p. 132-137°C.

MS (Cl, +ion): 550 (M+H).

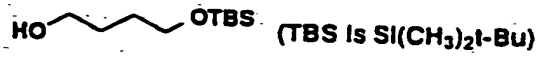
Anal. Calc. for $C_{32}H_{35}ClF_3N_3O_2 \cdot 0.2\ H_2O$:
C, 65.18; H, 6.05; N, 7.13; Cl, 6.01;
F, 9.66
Found: C, 65.45; H, 6.06; N, 6.88; Cl, 5.16;
F, 9.30.

Example 37

2,3-Dihydro-2-[1-[4-[9-(1-oxopentyl)-9H-fluoren-9-yl]butyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

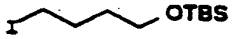
A.

A(1).



To a solution of 49 mL (0.55 mol) of 1,4-butanediol in 25 mL of DMF, under argon at 0°C, was added 10.5 g (0.15 mol) of imidazole followed by 20.7 g (0.14 mol) of t-butyldimethylsilyl chloride. The reaction was slowly warmed to RT and stirred for 18 h at which time the reaction was diluted with ether and washed with NH_4Cl, water, Na_2CO_3, brine and dried ($MgSO_4$). The resulting title compound in the form of a colorless liquid, 50 g, contained approximately 15% of the disilylated compound.

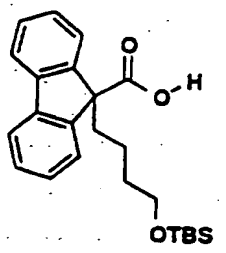
A(2).



To a solution of 8.5 g (42 mmol) of Part A(1) compound in 50 mL of THF, under argon at 0°C, was added 7.3 g (108 mmol) of imidazole and 16.7 g (64 mmol) of triphenylphosphine. This mixture was stirred for 45 min (solution became homogeneous) at which time 16.2 g (64 mmol) of iodine in 50 mL of THF was added dropwise over 20 min. The reaction was stirred for 1 h, diluted with hexanes and washed with 1M sodium bisulfite, Na_2CO_3, brine and dried (Na_2SO_4). The resulting residue was triturated with ether (3x), filtered (to remove triphenylphosphine oxide) and evaporated to provided 10 g (61%) of title compound as a pale yellow oil.

TLC Silica gel (4:1 hexanes/ethyl acetate)
R_f = 0.60.

B.

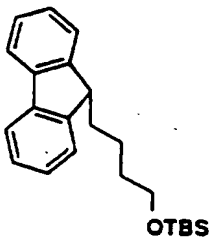


To a solution of 5 g (23.78 mmol) of 9-fluorenecarboxylic acid (Aldrich) in 20 mL of THF, under argon at 0°C, was added 20.6 mL (52.32 mmol) of n-butyllithium (2.5 M in hexanes) dropwise. The orange-red anion was stirred for 0.5 h, at which time 7.5 g (23.78 mmol) of 

(prepared as described in Part A) was added dropwise. The reaction gradually warmed to RT and was stirred for 36 h, at which time it was diluted with a 1:1 mixture of ethyl acetate/H_2O (250 mL). The organics were washed with $NaHCO_3$, brine, dried (Na_2SO_4) and evaporated. Flash chromatography was performed on 250 g of silica gel eluting with 9:1 dichloromethane/isopropanol to provide 4.9 g (52%) of title compound as a yellow oil.

TLC: Silica gel (9:1 dichloromethane/isopropanol) R_f = 0.50.

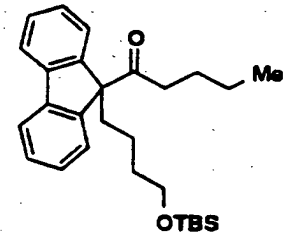
C.



To 550 mg (1.38 mmol) of Part B compound was added 5 mL of DMSO. The reaction was stirred for 18 h, under argon at RT, at which time it was diluted with ether and washed with water (3x). Flash chromatography was performed on 100 g of silica gel eluting with 95:5 hexanes/ethyl acetate to provide 340 mg (70%) of title compound as a pale yellow oil.

TLC: Silica gel (95:5 hexanes/ethylacetate)
R_f = 0.31.

D.



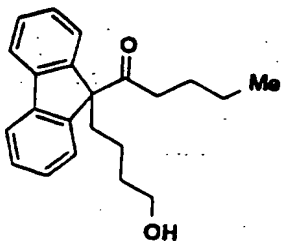
To a solution of 340 mg (0.96 mmol) of Part C compound in 3 mL of THF, under argon at 0°C, was added dropwise 462 mL (1.16 mmol) of n-butyllithium (2.5 M in hexanes). The resulting anion was stirred for 0.5 h, at which time 140 mL (1.16 mmol) of freshly distilled valeryl chloride (Aldrich) was added dropwise. The reaction was stirred for 2 h, at which time it was diluted with ether and quenched with $NaHCO_3$. The organics were washed with water, brine, dried ($NaSO_4$) and evaporated. Flash chromatography was performed on 100 g of silica gel eluting with 95:5 hexanes/dichloromethane to provide 290 mg (69%) of title compound as a pale yellow oil.

TLC: Silica gel (95:5 hexanes/ethyl acetate)
R_f = 0.36.

MS (CI-NH_3, + ions) m/e 397 (M+H).

Anal. Calcd. for $C_{24}H_{32}O_3Si$ + 0.15 mol H_2O:
C, 72.20; H, 8.15
Found: C, 72.20; H, 7.88.

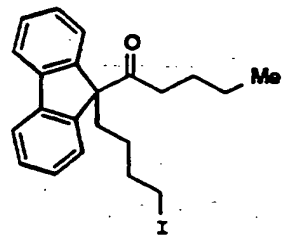
E.



To 200 mg (0.46 mmol) of Part D compound was added 1 mL of 5:95 aqueous HF/acetonitrile. The reaction was stirred under argon at RT, for 3 h, at which time it was diluted with ether and washed with $NaHCO_3$, water (3x), brine, dried ($MgSO_4$) and evaporated. Flash chromatography was performed on 50 g of silica gel eluting with 7:3 hexanes/ethyl acetate to provide 120 mg (81%) of title compound as a pale yellow oil.

TLC: Silica gel (8:2 hexanes/ethyl acetate)
R_f = 0.15.

F.



To a solution of 120 mg (0.37 mmol) of Part E compound in 1.5 mL of THF, under argon at 0°C, was added 55 mg (0.81 mmol) of imidazole followed by 126 mg (0.48 mmol) of triphenylphosphine. The mixture was stirred for 0.5 h, at which time 122 mg (0.48 mmol) of iodine in 1 mL of THF was added dropwise. The reaction was stirred for 1 h at 0°C, 1 h at RT, then diluted with hexanes and washed with fresh sodium bisulfite solution, $NaHCO_3$, water, brine, dried ($MgSO_4$) and evaporated. Flash chromatography was performed on 25 g of silica gel eluting with 9:1 hexanes/ethyl acetate to provide 130 mg (81%) of title compound as a colorless oil.

TLC: Silica gel (9:1 hexanes/ethyl acetate)
R_f = 0.40.

G. 2,3-Dihydro-2-[1-[4-[9-(1-oxopentyl)-9H-fluoren-9-yl]butyl]-4-piperidinyl]-1H-isoindol-1-one, monohydrochloride

To a solution of 130 mg (0.30 mmol) of Part F compound in 1.5 mL of DMF, under argon at RT, was added 20 mg (0.15 mmol) of K_2CO_3 and 84 mg (0.39 mmol) of Example 1 Part G compound. The reaction was stirred for 18 h, at which time it was poured into water. The precipitate was collected, dissolved into ether, dried (Na_2SO_4) and evaporarted to provide a

pale yellow solid. The solid was dissolved in ether and treated with 305 mL (0.30 mmol) of HCl (1 M in ether). The ether was decanted off, the solids collected and dried for 18 h (50°C under vacuum) to provide 115 mg (74%) of title compound as a pale yellow solid.

mp 96-100°C.
TLC: Silica gel (95:5 dichloromethane/isopropanol + 1% NH_4OH) R_f = 0.46.
MS (ES; NH_4OH, + ions) m/e 521 (M+H).

Anal. Calcd. for $C_{35}H_{40}N_2O_2$ HCl + 0.5 mol H_2O:
C, 74.25; H, 7.48; N, 4.95
Found: C, 74.24; H, 7.45; N, 4.98.

Example 38

2,3-Dihydro-2-[1-(1-oxo-3,3-diphenylpropyl)-4-piperidinyl]-1H-isoindol-1-one

To a solution of 3,3-diphenylpropionic acid (500 mg, 2.21 mmol) and DMF (1 drop) in dichloromethane (5 mL) at RT was added dropwise a solution of oxalyl chloride in dichloromethane (2.0M, 1.66 mL, 3.32 mmol). Bubbling of escaping gasses continued for 10 min after addition. The reaction was stirred at RT for 60 min, then concentrated in vacuo to give a crude oil. To a solution of crude acid chloride and triethylamine (1.4 mL, 10.0 mmol) in dichloromethane (10 mL) at 0°C under argon was added dropwise a solution of Example 1 Part G compound (434 mg, 2.00 mmol) in dichloromethane (2 mL). The reaction was stirred at 0°C for 10 min. Dichloromethane (100 mL) was added to dilute the

reaction and the resulting solution was washed with H_2O (40 mL), saturated sodium bicarbonate solution (40 mL), brine (40 mL) and dried over $MgSO_4$. Evaporation gave a crude gum. Purification was performed by flash chromatography on silica gel (100 g), loaded and eluted with 2.5% methanol in dichloromethane. Pure fractions were combined and evaporated to give title compound (610 mg, 72%) as a off-white solid.

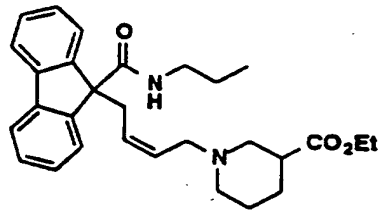
m.p. 166-169°C.
MS (FAB, +ion): 425 (M+H)

Anal. Calc. for $C_{28}H_{28}N_2O_2 \cdot 1.1\ H_2O$:
C, 75.68; H, 6.85; N, 6.30
Found: C, 75.50; H, 6.45; N, 6.24.

Example 39

[1-[4-[9-[(Propylamino)carbonyl]-9H-fluoren-9-yl]-butyl]-3-piperidinyl]carbamic acid, phenylmethyl ester, monohydrochloride

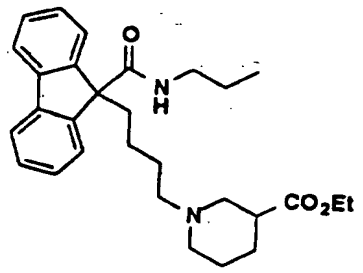
A.



A mixture of Example 5 Part A compound (2.34 g, 6.90 mmol) and ethyl nipecotate (1.3 mL, 8.28 mmol) in DMF (3.5 mL) under argon was heated at 60°C for 22 h, then cooled to RT. The solvent was removed under reduced pressure. The resulting orange residue was dissolved in CH_2Cl_2 (50 mL), washed with

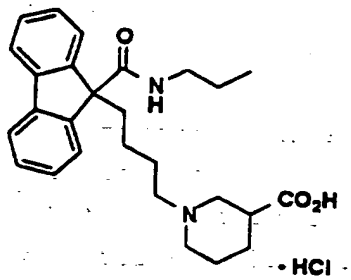
saturated $NaHCO_3$ (2 x 15 mL) and brine (20 mL), then dried over Na_2SO_4. Evaporation gave 3.6 g of an orange gum, which was dissolved in a minimal amount of CH_2Cl_2 and purified by flash chromatography on silica gel (175 g) eluting with 2% MeOH/CH_2Cl_2 to provide 2.65 g of product contaminated with approximately 20 mol% DMF. The product was dissolved in EtOAc (60 mL), washed with water (3 x 20 mL) and brine (20 mL), then dried over Na_2SO_4. Evaporation gave title compound (2.38 g, 75%) as an amber oil.

B.



Palladium on carbon (10%) (273 mg, 0.258 mmol) was added to a solution of Part A compound (2.37 g, 5.15 mmol) in a mixture of EtOAc (10 mL) and EtOH (15 mL). The mixture was hydrogenated (balloon) at RT for 1.5 h, filtered through Celite, and washed with EtOAc (3 x 20 mL). The filtrate was concentrated in vacuo to give title compound (2.42 g, 100%) as a pale yellow oil.

C.



Aqueous KOH (5.6 mL, 1N, 5.6 mmol) was added to a solution of Part B compound (2.17 g, 4.70 mmol) in THF (10 mL) under argon. The biphasic mixture was stirred at RT for 4 h, then heated at 50°C for 48 h. The reaction was cooled to RT and acidified to pH 1.5 with 1N HCl. The cloudy reaction was diluted with water (30 mL) and extracted with $CHCl_3$ (3 x 100 mL), then dried over Na_2SO_4. Evaporation afforded title compound (2.2 g, 100% crude) as a foamy white solid.

D. [1-[4-[9-[(Propylamino)carbonyl]-9H-fluoren-9-yl]-butyl]-3-piperidinyl]carbamic acid, phenylmethyl ester, monohydrochloride

To a cloudy suspension of Part C compound (336 mg, 0.714 mmol) and triethylamine (238 µL, 1.71 mmol) in dioxane under argon was added diphenylphosphoryl azide (184 µL, 0.857 mmol). The mixture was heated at 80°C for 2 h (N_2 evolution observed soon after heating commenced). Benzyl alcohol (367 µL, 3.57 mmol) was added, and the reaction was heated at 80°C overnight. The reaction was cooled to RT and the solvent was distilled off under reduced pressure. The resulting residue was partitioned between CH_2Cl_2 (20 mL) and saturated $NaHCO_3$ (5 mL). The organic layer was washed with brine (5 mL) and dried over Na_2SO_4. Evaporation gave 760 mg of a yellow oil,

which was purified by flash chromatography on silica gel (50 g) eluting with 3% MeOH/CH_2Cl_2 to give 215 mg of a colorless oil.

The free amine was dissolved in Et_2O (3 mL) and treated with 0.77N HCl in Et_2O (3 mL). The white precipitate was filtered, washed with Et_2O (2 x 3 mL), then dried under high vacuum at 50°C overnight to give title comound (173 mg, 42%) as a white foamy solid.

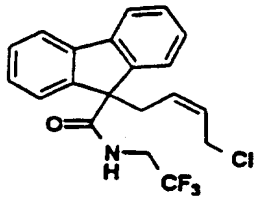
MS (ES) 540 [M+H]

Anal. Calcd. for $C_{34}H_{42}ClN_3O_3 \cdot 0.3\ H_2O$:
C, 70.22; H, 7.38; N, 7.23.
Found: C, 70.11; H, 7.24; N, 7.09.

Example 40

9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

A.

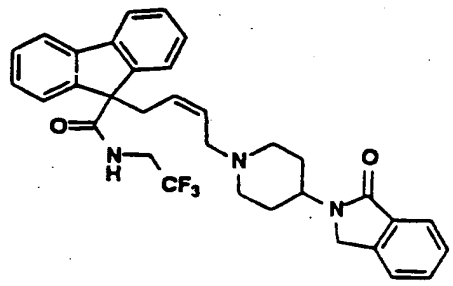


To a stirred solution of 10.0 g (33.5 mmol) of compound prepared in Example 5 Part A first paragraph in 100 mL of dichloromethane at RT was added 20.0 mL (40 mmol) of 2M oxalyl chloride in dichloromethane followed by 30 mL of DMF. The reaction was allowed to stir at RT for 2 h when the solvent was evaporated and the semisolid residue pumped (≈ 1 mm pressure) for 0.5 h. The residue was dissolved by adding 300 mL of ether and cooled to 0°C. The mixture was

treated with 7.30 g (67 mmol) of 2,2,2-trifluoroethylamine and warmed to room temperature. The mixture was diluted with 150 mL of ethyl acetate and 100 mL of 0.5 M HCL. The layers were separated, the organics dried (Na_2SO_4) and concentrated. The remainder was purified by flash column chromatography on silica gel (250 g) eluting with 1:9 ethyl acetate/hexanes (800 mL) followed by 1:5 ethyl acetate/hexanes (1L). Pure fractions were pooled and concentrated to give 9.25 g (73%) of title compound as a white solid.

mp: 87-89°C

B.



To a stirred solution of 6.54 g (17.22 mmol) of Part A compound in 6 mL of DMF at RT was added 4.00 g (18.51 mmol) of Example 1 Part G compound and 2.41 g (17.50 mmol) of K_2CO_3. The reaction mixture was warmed to 40° and allowed to stir for 20 h. The mixture was diluted with 200 mL of water and 2 mL of 1M NaOH solution (pH = 11). The white solids were collected by filtration and dried to give 10.0 g (100%) of title compound.

TLC Silica gel (5:95:1 methanol/dichloromethane/NH_3) R_f= 0.35.

C. 9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A suspension of 10.00 g (≈ 17 mmol) of Part B compound in 80 mL of ethanol was treated with 0.5 g of 10% Pd/carbon and placed under an atmosphere of H_2 (balloon pressure). The reaction mixture was stirred for 25 h when it was filtered through a pad of Celite and concentrated. The remainder was triturated with warm water to give 9.0 g (93%) of title compound as a white solid.

mp: 143-146°C.
TLC Silica gel (5:95:1 methanol/dichloromethane/NH_3) R_f= 0.35.

D. 9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

A suspension of 9.00 g (≈ 16 mmol) of Part B compound in 200 mL of ethyl ether was treated with 8 mL (32 mmol) of 4M HCl in dioxane and the reaction mixture stirred for 1h under an atmmosphere of N_2. The reaction mixture was filtered and the white solid collected. The solid was dried at 40°C under vaccuum to give 9.0 g (93%) of title compound as a white solid.

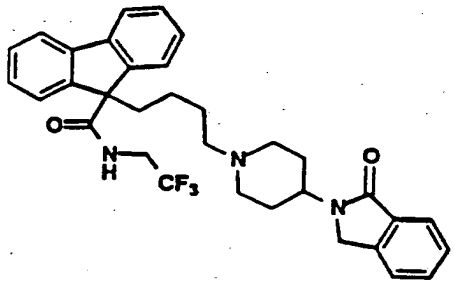
mp: 139-141°C.
TLC Silica gel (5:95:1 methanol/dichloromethane/NH_3) R_f= 0.35.
MS (ES, + ions) m/z 562 (M+H).

Anal. Calcd. for $C_{33}H_{35}N_3O_2F_3Cl$:
C, 66.27; H, 5.90; N, 7.03; F, 9.53
Found: C, 66.53; H, 5.82; N, 6.78, F, 8.99.

Example 41

9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

A.



To a stirred solution of 4.00 g (9.38 mmol) of Example 36 Part B compound in 6 mL of DMF at RT was added 2.44 g (18.51 mmol) of Example 2 Part A compound and 1.59 g (11.30 mmol) of K_2CO_3. The reaction mixture was warmed to 50°C and allowed to stir for 18 h. The mixture was diluted with 200 mL of water and 2 mL of 1M NaOH solution (pH=11). The white solids were collected by filtration and dried to give 4.50 g of title compound.

B. 9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, hydrochloride salt

A suspension of 4.00 g (= 9.00 mmol) of Part A compound in 200 mL of ethyl ether was treated with 8 mL (32 mmol) of 4M HCl in dioxane and the reaction mixture stirred for 1h under an atmosphere of N_2. The reaction mixture was filtered and the cream colored solid collected. The solid was dried at 40°C under vacuum to give 3.8 g (73%) of title compound.

mp: 139-141°C.
MS (ES, + ions) m/z 562 (M+H).

Anal. Calcd. for $C_{33}H_{35}N_3O_2F_3Cl$:
C, 66.27; H, 5.90; N, 7.03
Found: C, 65.87; H, 6.14; N, 6.71.

Examples 42-50

Following the procedures set out herein, the following compounds were prepared.

Example 42

9-[4-[3-(Benzoylamino)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide.

MS (ES) 510 (M+H)
Anal. Calcd. for $C_{33}H_{39}N_3O_2 \cdot 0.2\ H_2O$:
C, 77.22; H, 7.74; N, 8.19
Found: C, 77.12; H, 7.58; N, 8.16.

Example 43

9-[4-[3-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide.

MS (ES) 536 (M+H)
Anal. Calcd. for $C_{34}H_{37}N_3O_3 \cdot 0.2\ H_2O$:
C, 75.72; H, 6.99; N, 7.79
Found: C, 75.68; H, 6.78; N, 7.68.

Example 44

9-[4-[4-(2,3-Dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,3,3,4,4,4-heptafluorobutyl)-9H-fluorene-9-carboxamide, monohydrochloride.

mp: 122-132°C
MS (ES, + ions) m/z 662 (M+H)
Anal. Calcd. for $C_{35}H_{35}O_2N_3F_7Cl \cdot 0.8\ H_2O$:
C, 59.04; H, 5.17; N, 5.90
Found: C, 59.04; H, 5.04; N, 5.90.

Example 45

9-[4-[[4-[(1,1-Dimethylethoxy)carbonyl]amino]-1-piperidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

mp: 59-64°C
MS (FAB, M+H)$^+$= m/z 582$^+$
Anal. Calcd. for $C_{30}H_{36}F_5N_3O_3 \cdot 0.2$ equiv. hexane:
C, 62.58; H, 6.53; N, 7.02
Found: C, 62.41; H, 6.55; N, 6.84.

Example 46

1-[4-[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-2-methyl-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide.

mp: 124-126°C
MS m/z (ES, + ions) 526.3 (M+H)
Anal. Calcd. for $C_{30}H_{34}F_3N_3O_2$:
C, 67.55; H, 6.52; N, 7.99; F, 10.84
Found: C, 67.80; H, 6.53; N, 7.89; F, 10.75.

Example 47

9-[4-[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,3,3,3-pentafluoropropyl)-9H-fluorene-9-carboxamide, monohydrochloride.

mp: 130-144°C
MS (ES, + ions) m/z 578 (M+H)
Anal. Calcd. for $C_{34}H_{35}N_3O_2F_5Cl$ + 1.2 H_2O:
C, 60.98; H, 5.63; N, 6.27; F, 14.18
Found: C, 61.34; H, 5.48; N, 6.08; F, 13.69.

Example 48

1-[4-[4-(1,3-Dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide.

mp: 62-65°C
MS m/z (ES, - ions) 510 (M-H), 556 (M+HCO_2-)
Anal. Calcd. for $C_{29}H_{32}F_3N_3O_2$ • 0.16 H_2O:
C, 67.70; H, 6.33; N, 8.17; F, 11.08
Found: C, 67.70; H, 6.26; N, 7.94; F, 10.62.

Example 49

9-[4-[4-(Benzoylamino)-1-piperidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

MS (FAB, M+H)$^+$ m/z 586$^+$
Anal. Calcd. for $C_{32}H_{32}F_5N_3O_2 \cdot H_2O \cdot 0.15\ CH_2Cl_2$:
C, 62.65; H, 5.61; N, 6.82
Found: C, 62.52; H, 5.56; N, 6.67.

Example 50

3,6-Difluoro-9-[4-[4-[(2-phenoxybenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

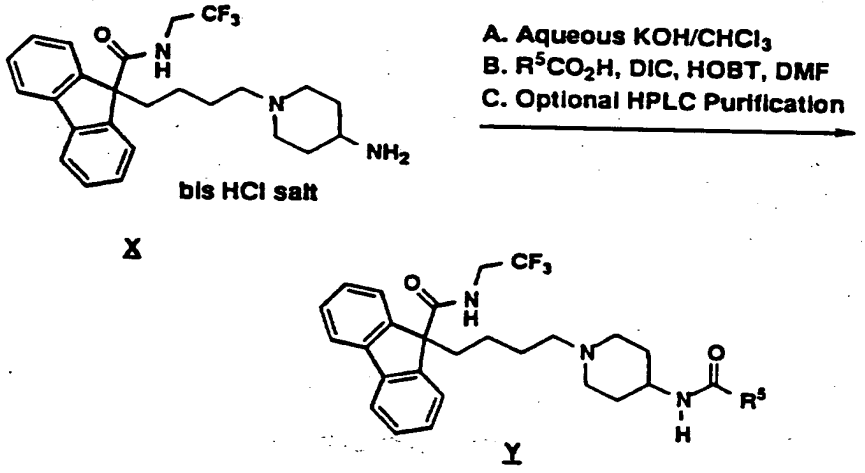
mp: 124-26°C
MS (FAB, M+H) m/z 678+
Anal. Calcd. for $C_{38}H_{36}F_5N_3O_3$:
C, 67.35; H, 5.35; N, 6.20
Found: C, 67.38; H, 5.62; N, 5.92.

Examples 51 to 167

The following compounds were prepared by robotics procedures as described below.

ROBOTICS PROCEDURES

Robotic Method for the Preparation of Amides



X Y

A. Preparation of the diamine starting material:

A solution of the diamine bishydrochloride salt (compound X) (10 g, 19.3 mmol) in chloroform

(400 mL) was washed with 1N KOH solution (3 x 100 mL). The organic layer was washed H_2O (2 x 100 mL), brine (2 x 100 mL) and dried over $MgSO_4$. Evaporation gave the free diamine (8.8 g, 100%) as a colorless oil.

B. General Experimental for Robotics Compounds:

The following is a general procedure for the synthesis of amides according to the above equation via the coupling of carboxylic acids with the diamine. These acid-amine couplings and subsequent purifications were carried out using a Zymark Benchmate® Robotic system using an IBM PC to run the operating program and to write the Benchmate procedures.

A 16 mm x 100 mm tube was charged with 1.6 mmol, 4 eq R^5CO_2H acid and capped loosely with a plastic cap/column holder. The Benchmate® then carried out the following steps on the tube:

1) Added 1 mL (81 mg, 0.6 mmol, 1.5 eq) of a 81 mg/mL solution of 1-hydroxybenzotriazole hydrate in DMF.

2) Added 1 mL (75 mg, 0.6 mmol, 1.5 eq) of a 75 mg/mL solution of diisopropylcarbodiimide in CH_2Cl_2.

3) Added 1 mL (178 mg, 0.4 mmol, 1 eq) of a 178 mg/mL solution of diamine in CH_2Cl_2.

4) Washed syringe with 3 mL of CH_2Cl_2

5) Mixed tube contents by vortexing at speed 3 for 15 sec.

After 12-48 h the reaction was complete (no starting amine remained as determined by TLC; 10% MeOH + 1% NH_4OH in CH_2Cl_2, I_2) .

The reaction mixture contents were then purified by ion exchange chromatography mediated by the Benchmate® Robot. The following is the standard procedure developed for purification of the coupled products by the Benchmate®:

1) Condition a Varian solid phase extraction column (1.5 g, SCX cation exchange) with 10 mL of MeOH at 0.25 ml/sec

2) Load reaction contents onto column at 0.05 mL/sec

3) Wash column with 2 x 10 mL of MeOH at 0.1 ml/sec

4) Wash column with 10 mL of 0.1 M ammonia in MeOH at 0.1 ml/sec

5) Elute column with 4 mL of 2 M ammonia in MeOH and collect into a tared receiving tube at 0.1 ml/sec

6) Elute column with 1 mL of 2 M ammonia in MeOH and collect into same tared receiving tube at 0.1 ml/sec

7) Rinse syringe with 5 mL of MeOH

All solution/solvent deliveries were followed by 1.8 mL of air and 10 sec push delay was used after loading reaction contents onto the ion exchange column.

The product solution was concentrated on a Savant Speed Vac (approx. 2 mm Hg for 5 h) and final solvent remnants were removed by further exposure to

high vac (0.015 mm Hg, 14 h) to afford product Y, which was characterized by HPLC and MS.

MS (ES, + ions) m/z 619 (M + H)

C. Preparative HPLC Purification

In cases where the coupling reaction is carried out with carboxylic acids bearing basic substituents (for example, pyridyl or amino), the product Y isolated as above in Part B, is contaminated with the starting acid. These materials were further purified by preparative HPLC.

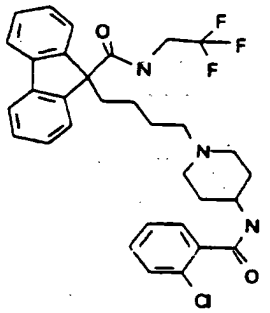
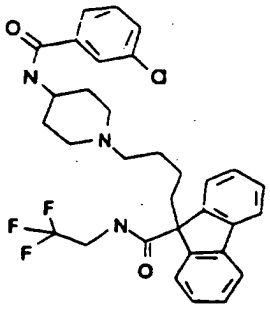
The samples after elution from the SCX column and speed vac concentration were reconstituted in MeOH and a small amount of trifluoroacetic acid (1 drop) was added to each. The products Y were purified by preparative chromatography using the following conditions:

Solvent A: 10% MeOH, 90% H_2O, 0.1% TFA
Solvent B: 90% MeOH, 10% H_2O, 0.1% TFA
Column: YMC ODS-A, SH-363-5, 30 x 250 mm I.D. S-5 µm, 120 A, No. 3025356A.

Starting % B:	0%
Final % B:	100%
Gradient time:	30 min
Flow rate:	25 mL/min
Wavelength:	220 nm
Attenuation:	9 (1.28 AUFS)

Pure fractions were combined and concentrated to afford purified product Y, which was characterized by HPLC + MS.

Please note that in the Examples 51 to 167, for structures bearing only two single bonded substituents to nitrogen, the third substituent is always hydrogen, but it is not shown explicitly in the structures. Also, please note that in the Examples 51 to 167 for structures bearing oxygens and sulfurs with only one single bonded substituent, the second substituent is always hydrogen, but is not shown explicitly in the structures.

Example No.	Molecular Structure	Analytical Data
51		m/z 585 (M+H)
52		m/z 585 (M+H)

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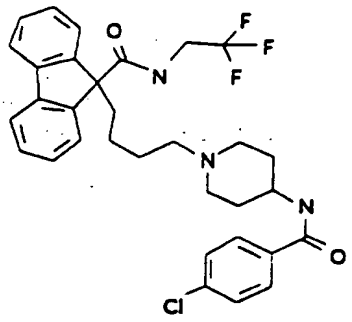
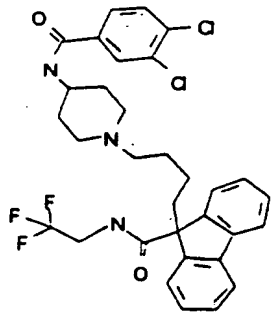


m/z 585
(M+H)

54



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(M+H)

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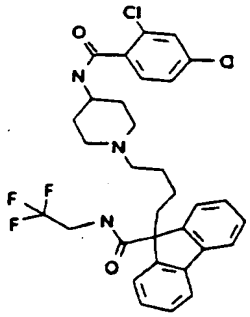
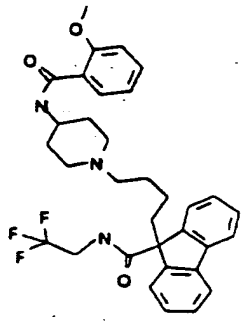
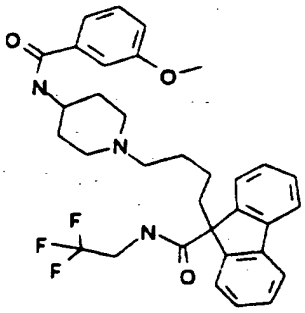
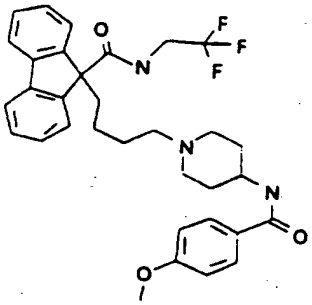
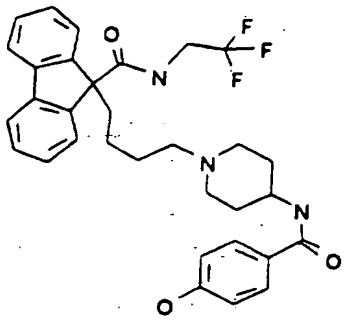


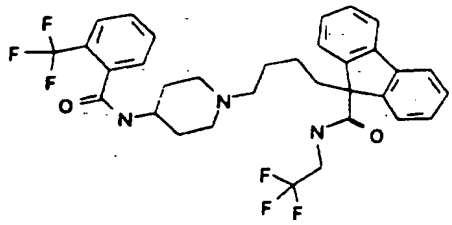
m/z 619
(M+H)

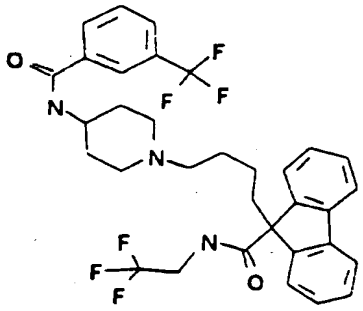
56  m/z 580 (M+H)

57  m/z 580 (M+H)

58  m/z 580 (M+H)

59  m/z 563 (M-H)

60  m/z 618 (M+H)

61  m/z 618 (M+H)

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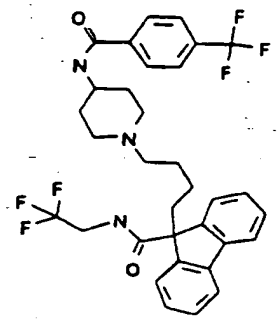
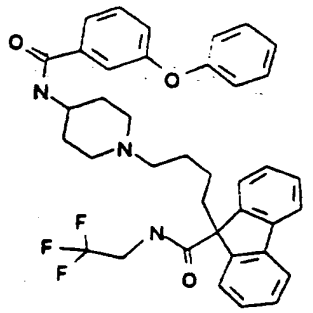


m/z 618
(M+H)

63



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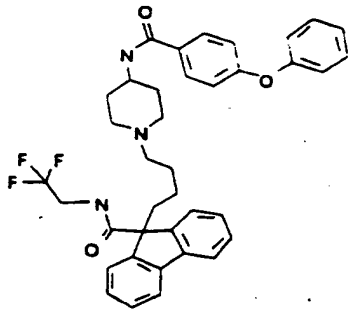

m/z 642
(M+H)

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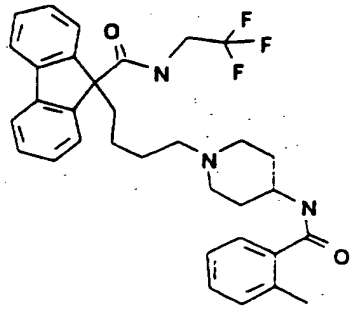

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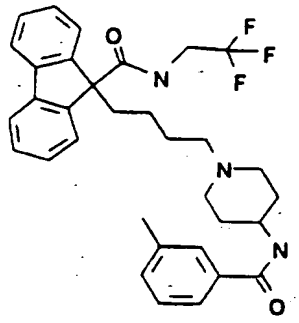
66 

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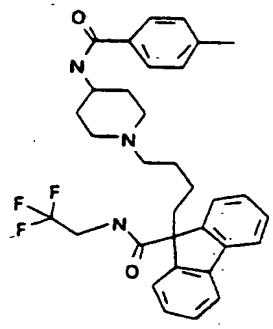
67 

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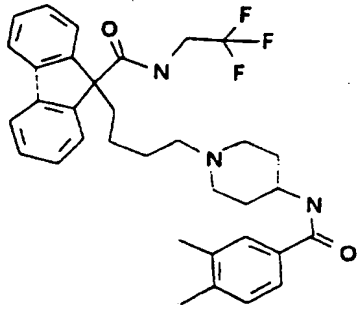
68 

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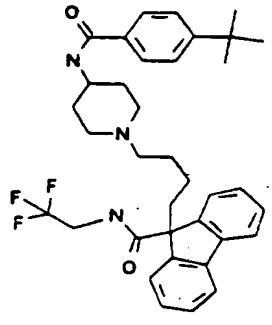
(M+H)

69 

m/z 606
(M+H)

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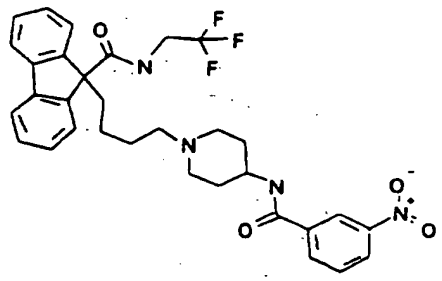

m/z 595
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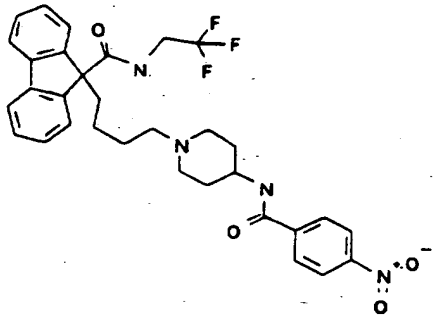

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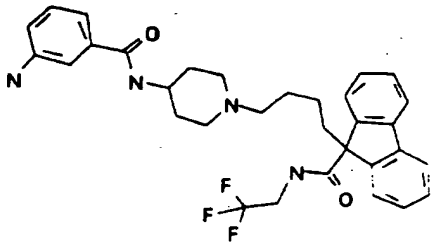

m/z 563
(M-H)

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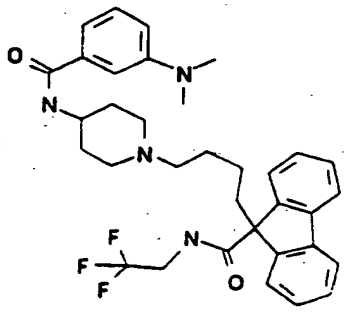

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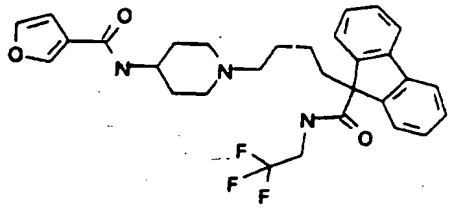
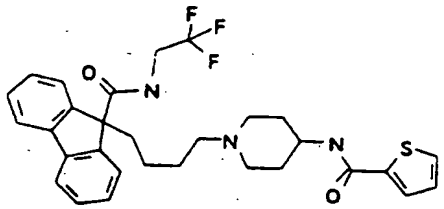
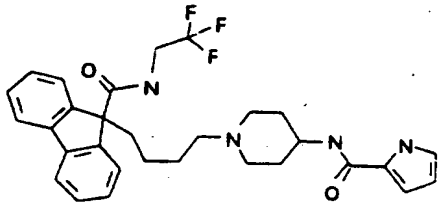
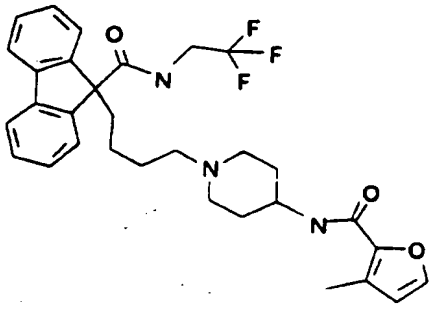
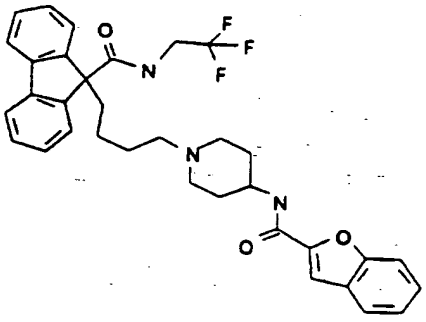
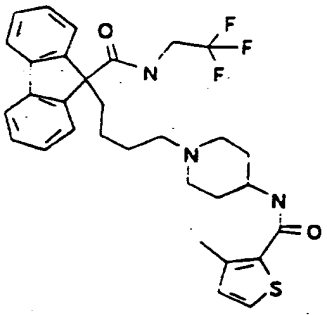
74  m/z 540 (M+H)

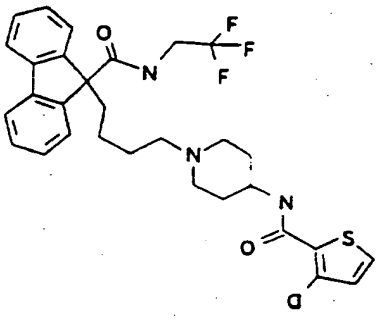
75  m/z 556 (M+H)

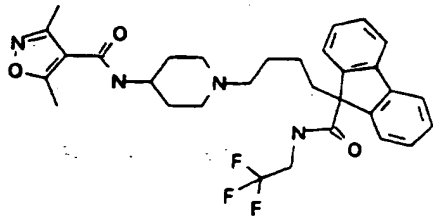
76  m/z 539 (M+H)

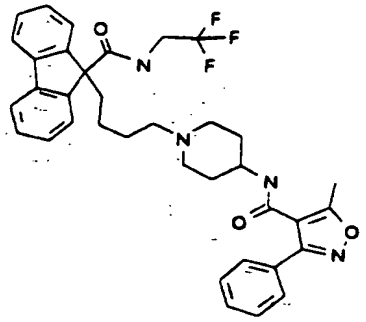
77  m/z 554 (M+H)

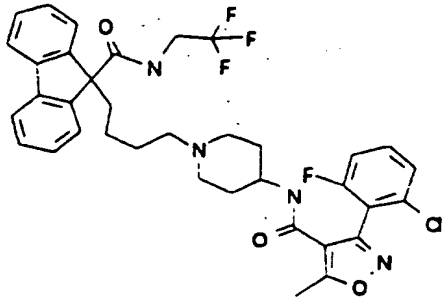
78  m/z 590 (M+H)

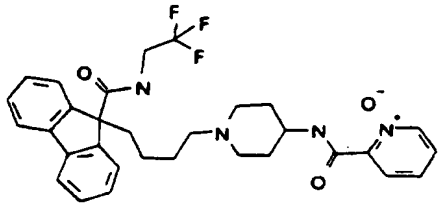
79  m/z 570 (M+H)

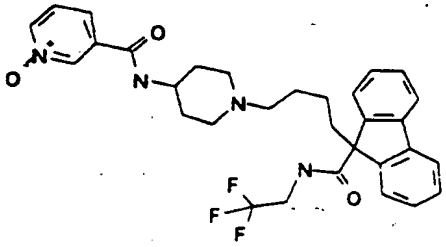
80  m/z 591 (M+H)

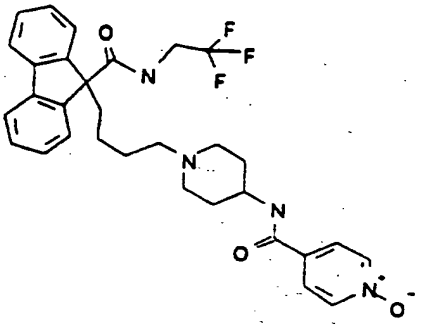
81  m/z 569 (M+H)

82  m/z 631 (M+H)

83  m/z 684 (M+H)

84  m/z 567 (M+H)

85  m/z 565 (M-H)

86 

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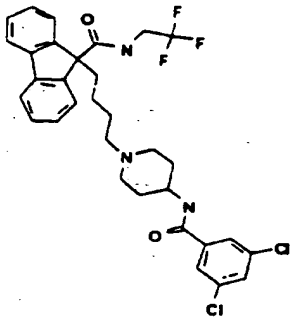
87 

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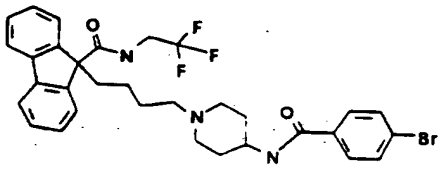
88 

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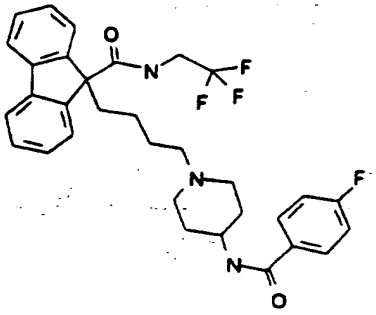
89 

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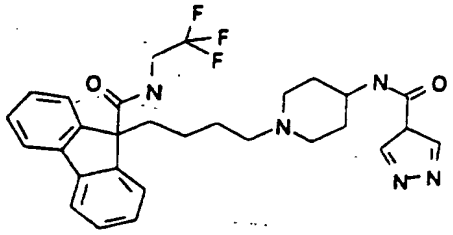
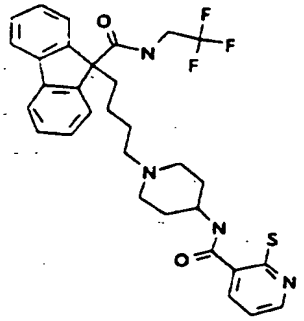
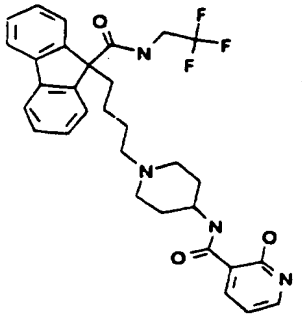
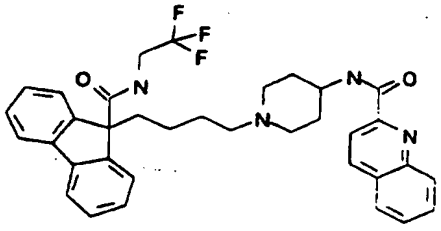
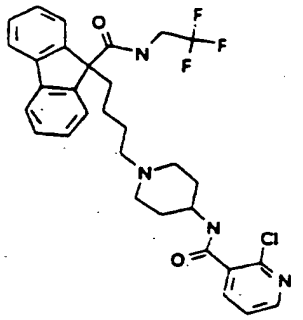
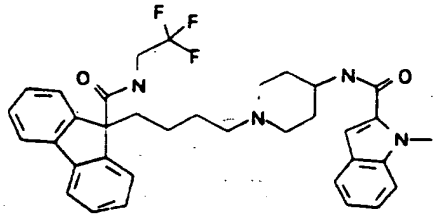
90  m/z 540 (M+H)

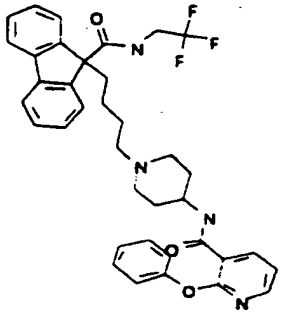
91  m/z 583 (M+H)

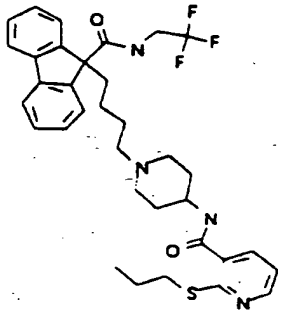
92  m/z 567 (M+H)

93  m/z 601 (M+H)

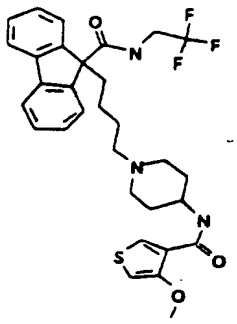
94  m/z 586 (M+H)

95  m/z 603 (M+H)

96  m/z 643 (M+H)

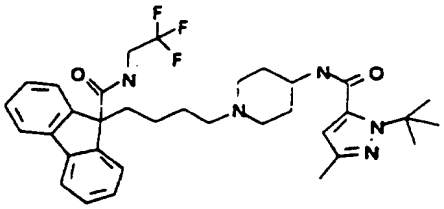
97  m/z 625 (M+H)

98



m/z 587
(M+H)

99



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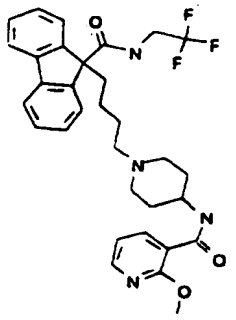
100



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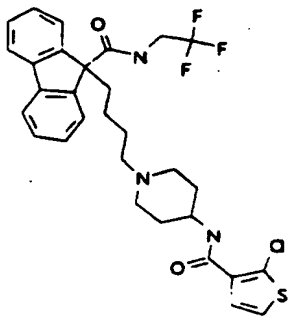

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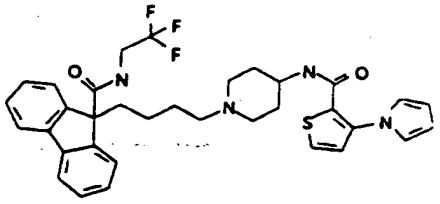
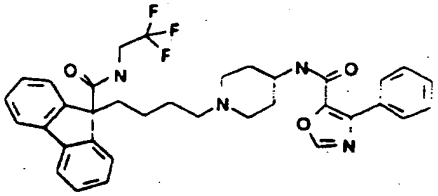
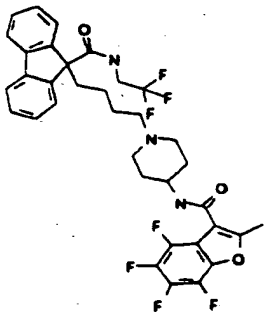
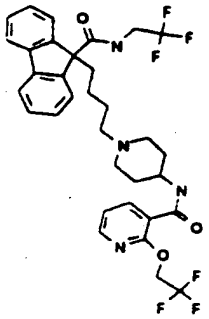
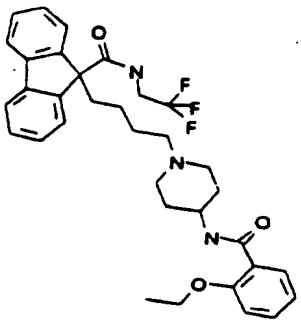
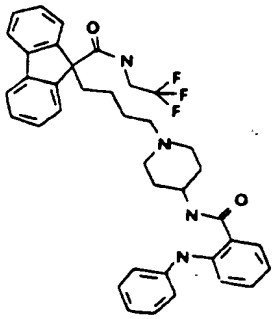
102  m/z 621 (M+H)

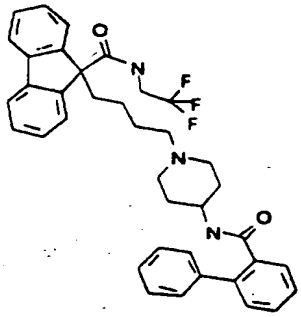
103  m/z 617 (M+H)

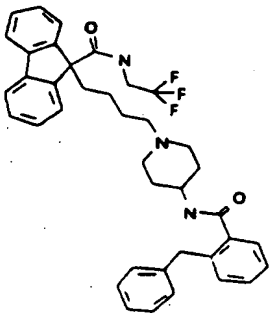
104  m/z 676 (M+H)

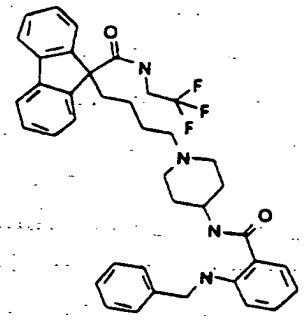
105  m/z 649 (M+H)

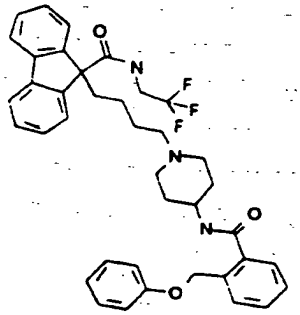
106  m/z 594 (M+H)

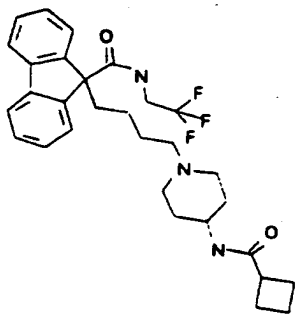
107  m/z 641 (M+H)

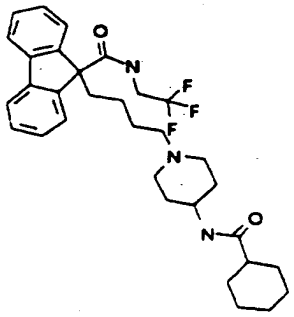
108  m/z 626 (M+H)

109  m/z 640 (M+H)

110  m/z 655 (M+H)

111  m/z 656 (M+H)

112  m/z 528 (M+H)

113  m/z 556 (M+H)

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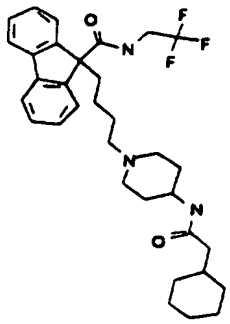

m/z 570
(M+H)

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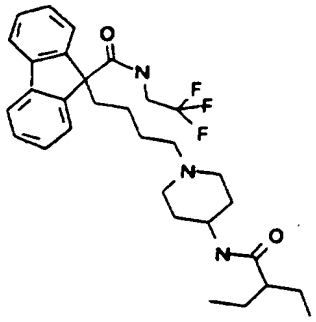
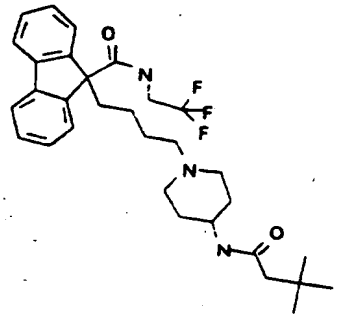


m/z 544
(M+H)

116



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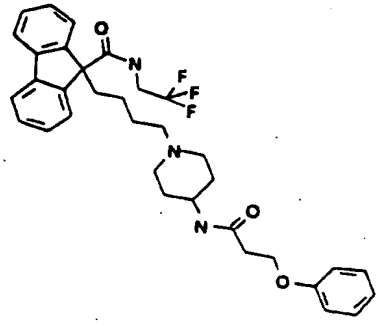
117



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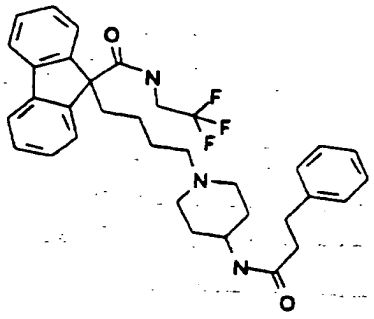
118 

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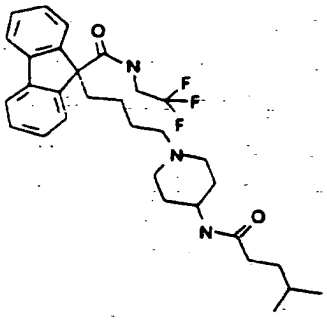
119 

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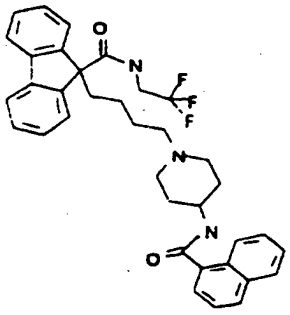
120 

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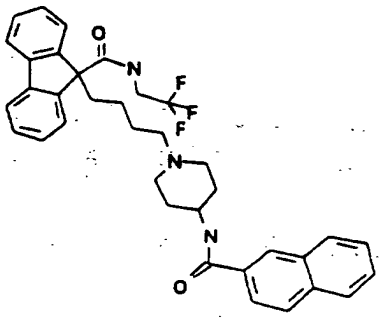
121 

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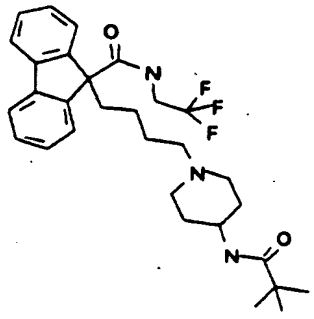
122



m/z 530
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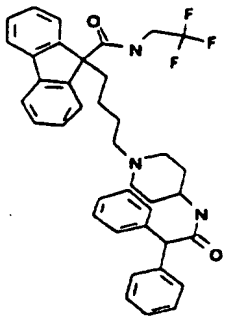
123



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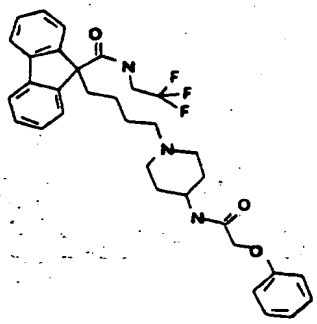
124



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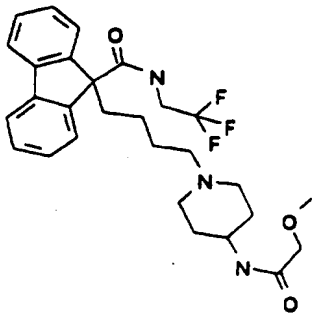
125



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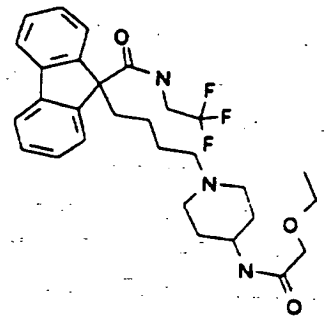
126



m/z 532
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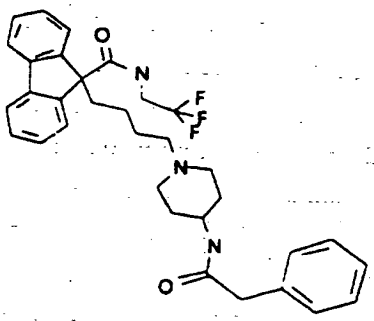
127



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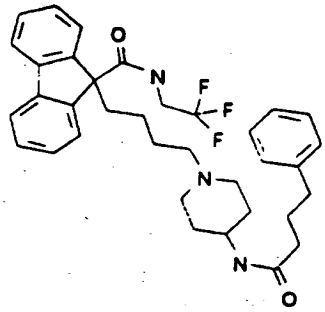
128



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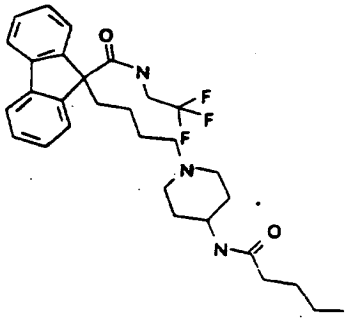
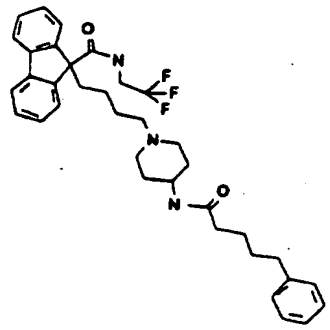
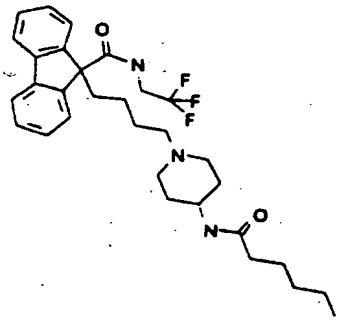
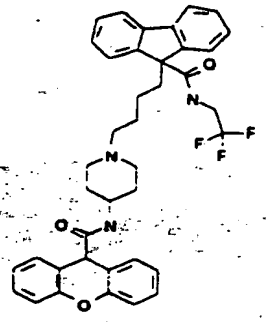
129

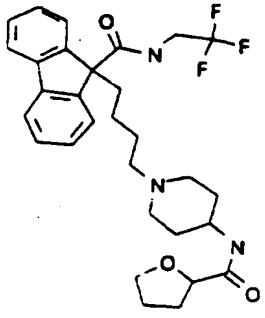


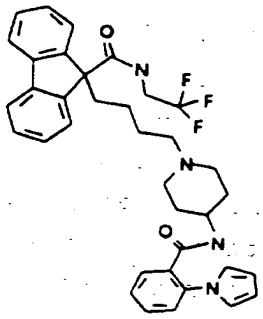
m/z 530
(M+H)

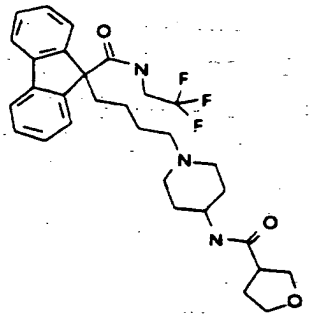
130  m/z 606 (M+H)

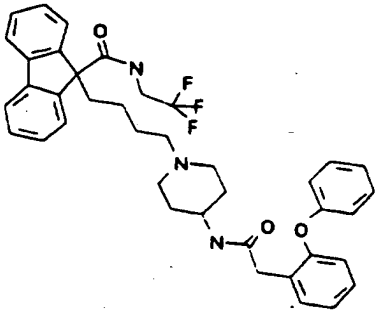
131  m/z 544 (M+H)

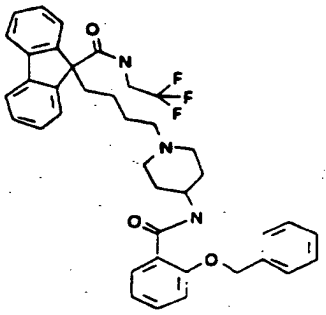
132  m/z 654 (M+H)

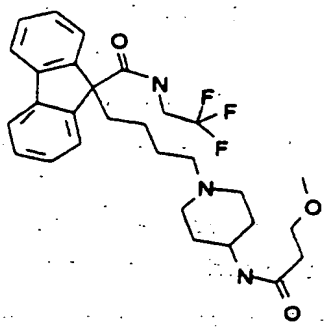
133  m/z 545 (M+H)

134  m/z 615 (M+H)

135  m/z 544 (M+H)

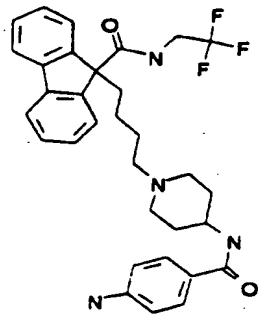
136  m/z 656 (M+H)

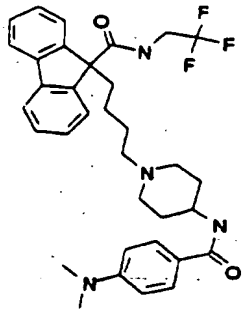
137  m/z 656 (M+H)

138  m/z 532 (M+H)

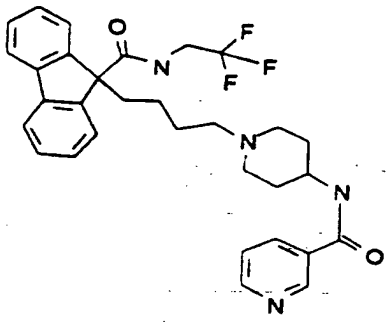
Examples 139 to 167

In the following Examples, the compounds prepared were purified by preparative HPLC (Method C) and isolated as trifluoroacetic acid salts.

139  m/z 565 (M+H)

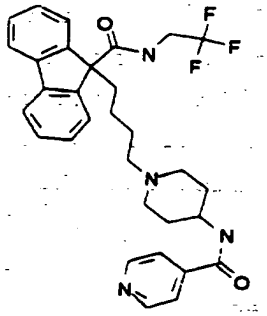
140  m/z 593 (M+H)

141



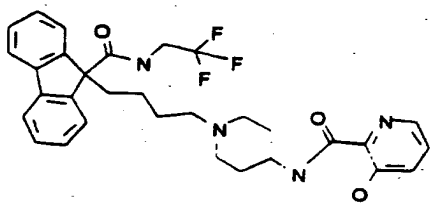
m/z 551
(M+H)

142



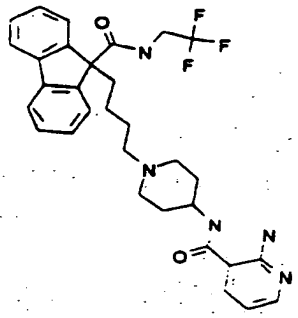
m/z 551
(M+H)

143



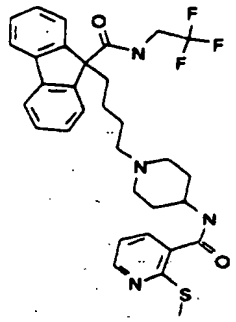
m/z 567
(M+H)

144



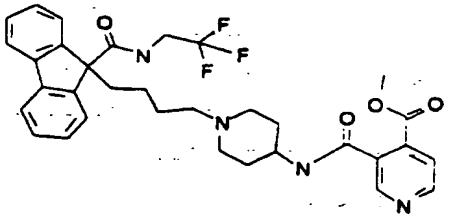
m/z 566
(M+H)

145



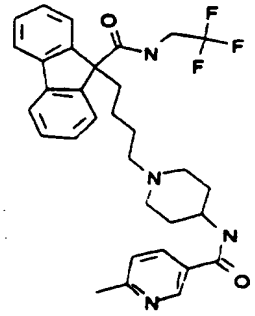
m/z 597
(M+H)

146



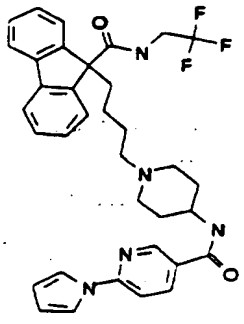
m/z 609
(M+H)

147

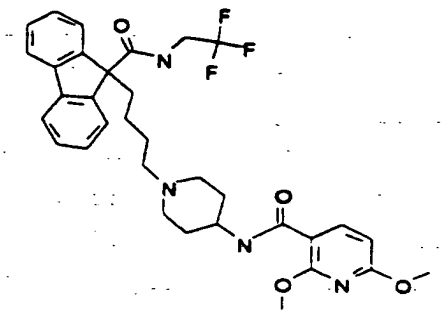


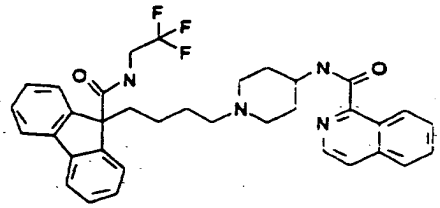
m/z 565
(M+H)

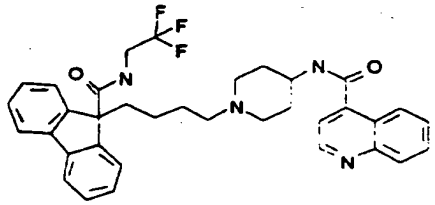
148

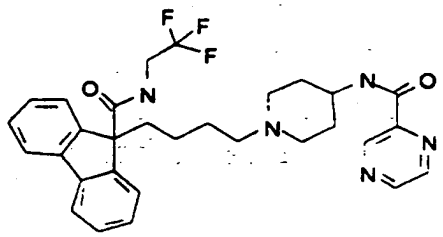


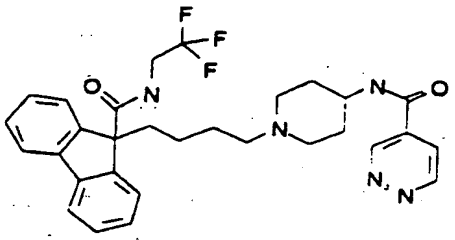
m/z 616
(M+H)

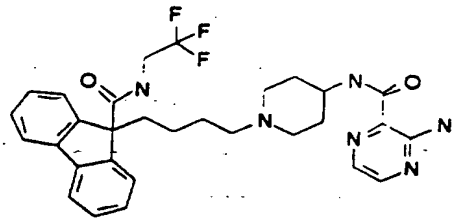
149  m/z 611 (M+H)

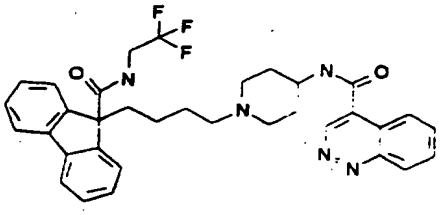
150  m/z 601 (M+H)

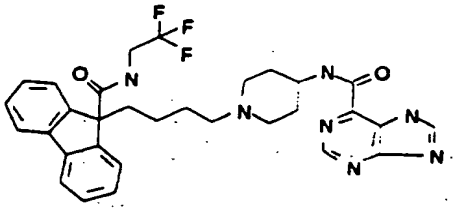
151  m/z 601 (M+H)

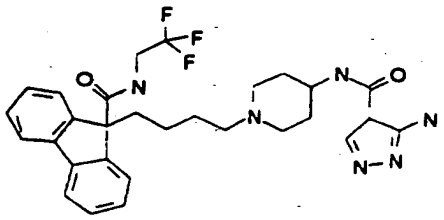
152  m/z 552 (M+H)

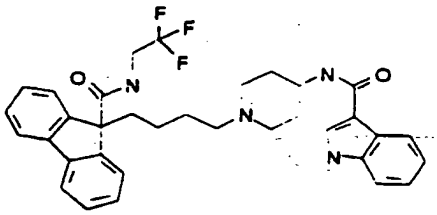
153  m/z 552 (M+H)

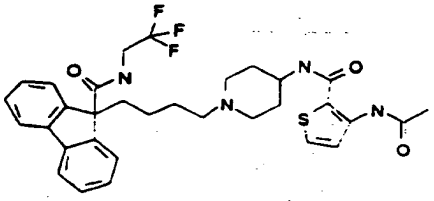
154  m/z 567 (M+H)

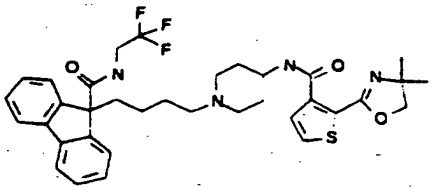
155  m/z 602 (M+H)

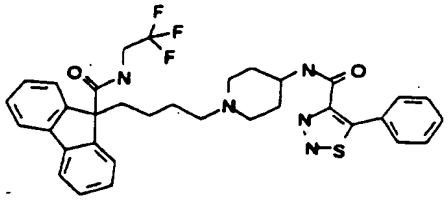
156  m/z 592 (M+H)

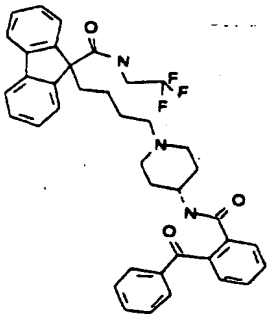
157  m/z 555 (M+H)

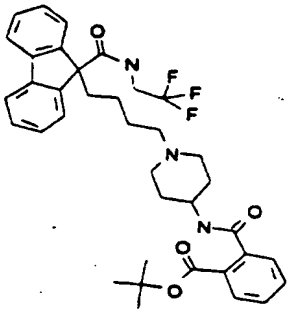
158  m/z 589 (M+H)

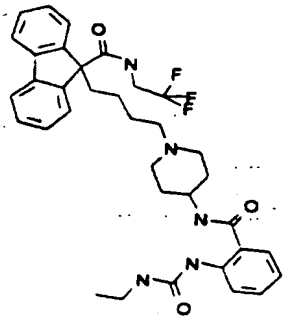
159  m/z 613 (M+H)

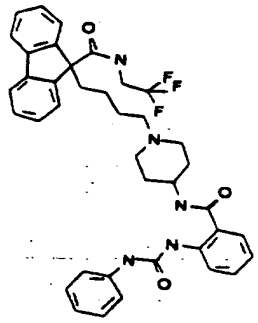
160  m/z 670 ($M+NH_4$)

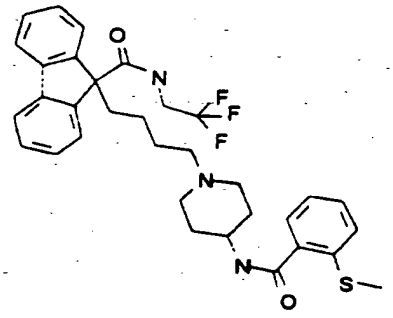
161  m/z 634 (M+H)

162  m/z 654 (M+H)

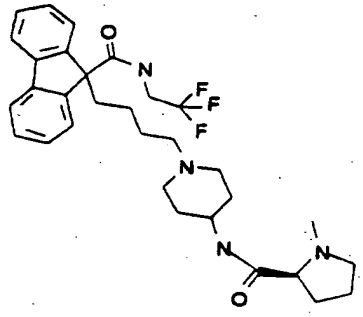
163  m/z 650 (M+H)

164  m/z 636 (M+H)

165  m/z 684 (M+H)

166  m/z 596 (M+H)

Chiral

167  m/z 557 (M+H)

Example 168

9-[4-[4-[(Phenoxycarbonyl)amino]-1-piperidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

To a solution of Example 36 Part D amine (500 mg, 0.96 mmol) and triethylamine (0.33 mL, 2.4 mmol)

in dichloromethane (5 mL) at 0°C was added dropwise phenyl chloroformate (0.14 mL, 1.06 mmol). The reaction was warmed to RT and stirring was continued for 1 h. Dichloromethane (100 mL) was added and the solution was washed with saturated sodium bicarbonate (2 x 30 mL), water (2 x 30 mL), brine (2 x 30 mL) and dried over $MgSO_4$. Evaporation gave a yellow oil. Purification was performed by flash chromatography on silica gel (100 g), loaded and eluted with 5% methanol in dichloromethane. Pure fractions were combined and evaporated to give a colorless oil. The resulting product was dissolved in methanol (1 mL) and a solution of hydrochloric acid in ethyl ether (1.1M, 1.1 mL) was added. The reaction was stirred at RT for 10 min, then evaporated to dryness. The product was dried in a vacuum oven (50°C, 24 h) to give title compound (300 mg, 53%) as a white solid.

m.p. 197-200°C
MS (ES, +ion): 566 (M+H)
Anal. Calc. for $C_{32}H_{35}ClF_3N_3O_3 \cdot 0.6\ H_2O$:
C, 62.71; H, 5.95; N, 6.86; F, 9.30
Found: C, 62.79; H, 5.88; N, 6.50; F, 9.10

Example 169

9-[4-[4-[[(Phenylamino)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

To a solution of Example 36 Part D amine (500 mg, 0.96 mmol) and triethylamine (0.33 mL, 2.4 mmol) in dichloromethane (5 mL) at 0 °C was added dropwise phenyl isocyanate (0.10 mL, 1.06 mmol). The reaction was warmed to RT and stirring was continued for 1 h.

Dichloromethane (100 mL) was added and the solution was washed with saturated sodium bicarbonate (2 x 30 mL), water (2 x 30 mL), brine (2 x 30 mL) and dried over $MgSO_4$. Evaporation gave a yellow oil. Purification was performed by flash chromatography on silica gel (100 g), loaded and eluted with 5% methanol in dichloromethane. Pure fractions were combined and evaporated to give a colorless oil. The resulting product was dissolved in methanol (2 mL) and a solution of hydrochloric acid in ethyl ether (1.1M, 1.1 mL) was added. The reaction was stirred at RT for 10 min, then evaporated to dryness. The product was dried in a vacuum oven (55°C, 24 h) to give title compound (200 mg, 40%) as a white solid.

m.p. 145-150°C
MS (CI, + ion): 565 (M+H)
Anal. Calc. for $C_{32}H_{36}ClF_3N_4O_2 \cdot 0.6\ H_2O$:
C, 62.81; H, 6.13; N, 9.16; F, 9.31
Found: C, 62.83; H, 6.05; N, 9.20; F, 9.27

Example 170

9-[4-[4-[(Phenylsulfonyl)amino]-1-piperidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

To a solution of Example 36 Part D amine (500 mg, 0.96 mmol) and triethylamine (0.46 mL, 3.36 mmol) in dichloromethane (5 mL) at 0°C was added dropwise benzenesulfonyl chloride (0.13 mL, 1.06 mmol). The reaction was warmed to RT and stirring was continued for 1 h. Dichloromethane (100 mL) was added and the solution was washed with saturated sodium bicarbonate (2 x 30 mL), water (2 x 30 mL), brine (2 x 30 mL) and

dried over $MgSO_4$. Evaporation gave a yellow oil. Purification was performed by flash chromatography on silica gel (100 g), loaded and eluted with 5% methanol in dichloromethane. Pure fractions were combined and evaporated to give a colorless oil. The resulting product was dissolved in methanol (2 mL) and a solution of hydrochloric acid in ethyl ether (1.1M, 1.1 mL) was added. The reaction was stirred at RT for 10 min, then evaporated to dryness. The product was dried in a vacuum oven (55°C, 24 h) to give title compound (400 mg, 71%) as a white solid.

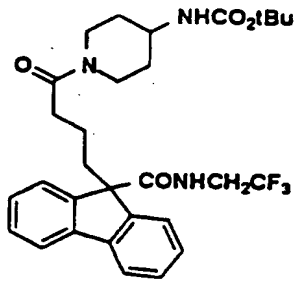
m.p. 130-134°C

MS (ES, + ion): 586 (M+H)

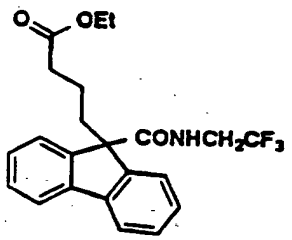
Anal. Calc. for $C_{31}H_{35}ClF_3N_3SO_3 \cdot 0.8\ H_2O$:
C, 58.59; H, 5.65; N, 6.61; Cl, 5.58; F, 8.97

Found: C, 58.77; H, 5.66; N, 6.40; Cl, 5.95; F, 9.03.

Example 171



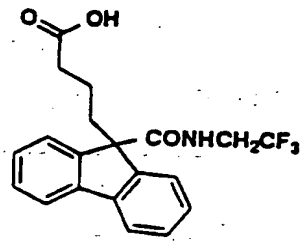
A.



To a solution of 1.05 g (5.00 mmol) of 9-fluorenecarboxylic acid in 15 mL of THF under argon (evacuated and purged with argon three times) at -10°C, was added 4.0 mL of n-butyllithium (10.0 mmol, 2.5 M in hexanes) over 10 min. A thick slurry formed initially followed by a yellow solution. After 30 min, 0.75 mL (7.0 mmol) of ethyl bromobutyrate was added. The reaction was allowed to warm to room temperature. After 24 h, the reaction was quenched with 10% citric acid solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. The residue was dissolved in 15 mL of dichloromethane and stirred at room temperature under argon while 7.5 mL of oxalyl chloride solution (2 M in dichloromethane, 15 mmol) was added, followed by DMF (100 µL). After 1 h, the resulting solution was evaporated at less than 30°C and the residue was then redissolved in 15 mL of THF. This solution was added to a solution of 2,2,2-trifluoroethylamine (1.1 g, 11 mmol) in 10 mL of THF under argon at 0°C. After 1 h, the reaction was quenched with 10% citric acid solution and extracted twice with ethyl acetate. The extracts were combined, dried ($MgSO_4$) and evaporated. Purfication by flash chromatography on silica gel (5 x 15 cm column, 3:97 ether/dichloromethane as elutant)

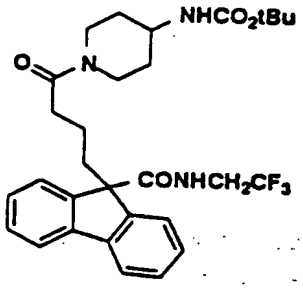
provided title compound as a white solid, 956 mg, 47% yield , mp 108-110°C.

B.



To a solution of Part A compound (580 mg, 1.43 mmol) in 5 mL of methanol at room temperature under argon was added a solution of lithium hydroxide hydrate (130 mg, 3.0 mmol) in 5 mL of water. The reaction mixture was stirred for 14 h and then partially evaporated to remove methanol. The reaction was quenched with 10% citric acid solution and extracted twice with ethyl acetate. The extracts were combined, dried ($MgSO_4$) and evaporated to give title compound as a white solid, 540 mg. It was used in the next step without further purification.

C.



To a solution of Part B compound (530 mg, 1.41 mmol), Example 10 Part B amine (280 mg, 1.41 mmol) and HOAt (210 mg, 1.5 mmol) in 5 mL of THF at room temperature under argon, was added DCC (295 mg, 1.43

mmol). After 15 h, the reaction was quenched with 10% citric acid and extracted twice with ethyl acetate. The extracts were combined, washed once with water, once with saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, 1:2 ethyl acetate/dichloromethane as elutant) provided title compound as a white solid, 625 mg, 79% yield, mp 90-92°C.

Anal. Calc. for $C_{30}H_{36}F_3N_3O_4 \cdot H_2O$:
C, 62.38; H, 6.63; F, 9.87; N 7.27
Found: C, 62.41; H, 6.24; F, 9.78; N 7.14.
MS (electrospray, - ions) m/e 558 (M-H).

Example 172

cis-9-[4-[4[(2-Phenoxybenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide

To a solution of Example 32 free amine (290 mg, 0.452 mmol) in CH_2Cl_2 (5 mL) at 0°C under argon was added a solution of 3-chloroperoxybenzoic acid (80-85%) (82 mg, 0.407 mmol) in CH_2Cl_2 (1.5 mL) slowly over 5 min. The reaction mixture was stirred at 0°C for 10 min, then saturated aqueous $NaHCO_3$ (1 mL) was added. The reaction mixture was stirred at 0°C vigorously for 1 h, diluted with CH_2Cl_2 (10 mL), washed with brine (5 mL), and then dried over Na_2SO_4. Evaporation gave 320 mg of a

white foam, which was purified by flash chromatography on silica gel (50 g) eluting with step gradient of 3% to 5% MeOH/CH_2Cl_2 to provide title compound (74 mg, 25%) as a white foamy solid.

MS (ES, + ions) m/z 658 (M+H)
Anal. Calcd for $C_{38}H_{38}F_3N_3O_4 + H_2O$:
C, 67.54; H, 5.97; N, 6.22; F, 8.43
Found: C, 67.61; H, 5.65; N, 6.18; F, 8.21.

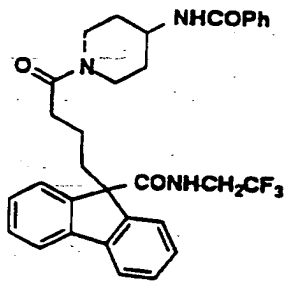
Example 173

9-[4-[4-[(2-Phenoxybenzoyl)amino]-1-piperidinyl]-4-oxobutyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A solution of Example 171 compound (2.00 g, 3.59 mmol) in 10 mL of 4 N hydrogen chloride in dioxane was stirred, protected by a calcium chloride drying tube, for 3 h. The solution was evaporated at 30°C and the resulting solid was re-dissolved in 10 mL of dichloromethane. To one-half of this solution (by weight), cooled to -10°C under argon, was added triethylamine (0.75 mL, 5.4 mmol) and then 500 mg of 2-phenoxybenzoyl chloride (2.15 mmol) over 10 min. After 1 h, the reaction was quenched with saturated sodium bicarbonate solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. Purfication by flash chromatography on silica gel (5 x 15 cm column, 1:9 hexanes/ethyl acetate as elutant) provided, after recrystal-lization from ethyl acetate/hexanes, title compound as a white solid, 745 mg, 63% yield , mp 96-98°C.

Anal. Calcd for $C_{38}H_{36}F_3N_3O_4 + H_2O$:
C, 67.74; H, 5.69; F, 8.46; N, 6.24.
Found: C, 67.84; H, 5.61; F, 8.63; N, 6.00.
MS (electrospray, + ions) m/z 656.3 (M+H), 673.3 ($M+NH_4$).

Example 174



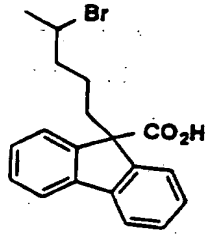
A solution of Example 171 compound (2.00 g, 3.59 mmol) in 10 mL of 4 N hydrogen chloride in dioxane was stirred, protected by a calcium chloride drying tube, for 3 h. The solution was evaporated at 30°C and the resulting solid was re-dissolved in 10 mL of dichloromethane. To one-half of this solution (by weight), cooled to -10°C under argon, was added triethylamine (0.75 mL, 5.4 mmol) and then 0.25 mL of benzoyl chloride (2.2 mmol) over 10 min. After 1 h, the reaction was quenched with saturated sodium bicarbonate solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. Purfication by flash chromatography on silica gel (5 x 15 cm column, 1:9 hexanes/ethyl acetate as elutant) provided, after recrystallization from ethyl acetate/hexanes, title compound as a white solid, 725 mg, 71% yield, mp 204-206°C.

Anal. Calcd for $C_{32}H_{32}F_3N_3O_3$:
C, 68.19; H, 5.72; F, 10.11; N, 7.46.
Found: C, 68.14; H, 5.73; F, 10.33; N, 7.40.
MS (electrospray, - ions) m/z 437 ($M-CF_3CH_2NHCO$), 562 (M-H).

Example 175

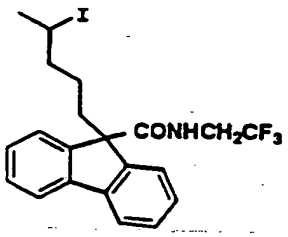
9-[4-[4-[[(1,1-Dimethylethoxy)carbonyl]amino]-1-piperidinyl]pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A.



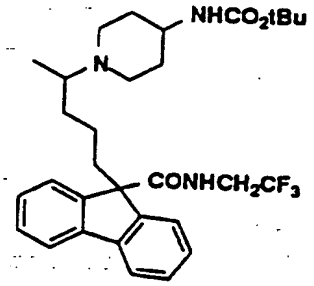
To a solution of 2.50 g (11.9 mmol) of 9-fluorenecarboxylic acid in 25 mL of THF under argon (evacuated and purged with argon three times) at -10°C, was added 10.0 mL of n-butyllithium (25.0 mmol, 2.5 M in hexanes) over 10 min. A thick slurry formed initially followed by a yellow solution. After 40 min, 2.05 mL (15.0 mmol) of 1,4-dibromopentane was added. The reaction was allowed to warm to room temperature. After 60 h, the reaction was quenched with 10% citric acid solution and extracted twice with ethyl acetate. The organic extract was dried ($MgSO_4$) and evaporated. Trituration of the residue in ethyl acetate/hexanes gave title compound as a white solid, 3.72 g, 87%.

B.



To a stirred solution of 1.80 g (*ca.* 5.0 mmol) of Part A compound in 10 mL of dichloromethane at room temperature under argon was added 0.65 mL of oxalyl chloride (7.5 mmol) followed by DMF (100 µL). After 1 h, the resulting solution was evaporated at less than 30 °C and the residue was then redissolved in 15 mL of dichloromethane. This solution was added to a solution of 2,2,2-trifluoroethylamine hydrochloride (820 mg, 6.0 mmol) and 2.1 mL of triethylamine (15 mmol) in 20 mL of dichloromethane under argon at 0°C. After 1 h, the reaction was quenched with 10% citric acid solution and extracted twice with ethyl acetate. The extracts were combined, dried ($MgSO_4$) and evaporated. The crude product was dissolved in 25 mL of 2-butanone, 7.7 g (52 mmol) of sodium iodide was added and the reaction mixture was set to reflux for 48 h under argon. The solution was cooled, evaporated and the residue partitioned between ethyl acetate and 10% sodium bisulfite solution. The organic extract was dried ($MgSO_4$) and evaporated. Purfication by flash chromatography on silica gel (5 x 15 cm column, 3:7 hexanes/dichloromethane as elutant) provided title compound as a white solid, 1.42 g, 58% yield , mp 102-106°C.

C.



A solution of Part B compound (1.27 g, 2.60 mmol), Example 10 Part B amine (680 mg, 3.38 mmol) and potassium carbonate (420 mg, 3.0 mmol) in 5 mL of DMF at room temperature under argon was heated to 50°C. After 15 h, the reaction was quenched with water, decanted and the oily residue extracted twice with ethyl acetate. The extracts were combined, washed once with water, once with saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, 1:99 methanol/ethyl acetate as elutant) provided title compound as a white solid, 1.20 g, 82% yield, mp 58-60°C.

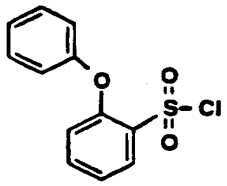
Anal. Calcd for $C_{31}H_{40}F_3N_3O_3$ + 0.25 H_2O:
C, 66.00; H, 7.24; F, 10.18; N, 7.45.
Found: C, 66.00; H, 7.14; F, 10.39; N, 7.60.
MS (electrospray, + ions) m/e 560.3 (M+H).

Example 176

9-[4-[4-[[(2-Phenoxyphenyl)sulfonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

To a solution of 2-phenoxyaniline (5.0 g, 27.0 mmol) in conc. hydrochloric acid (20 mL) and glacial acetic acid (6 mL) at -10°C, a solution of sodium

nitrite (2.01 g, 29.2 mmol) in water (3.5 mL) was added dropwise at such a rate that the reaction temperature did not exceed -5°C. The reaction was stirred at -5°C for 1 h. While the diazotization was being completed, sulfur dioxide was bubbled through glacial acetic acid (15 mL) until it was saturated. Cuprous chloride (0.75 g) was then added and the introduction of sulfur dioxide was continued until the yellow-green suspension became blue-green (30 min). The mixture was then cooled to 10°C and the solution containing the diazonium salt was added dropwise over 15 min. The green reaction mixture was warmed to RT and stirred for an additional 30 min, then poured into ice water (300 mL). Ethyl ether (200 mL) was added and the organic layer was washed with water (2 x 100 mL), saturated sodium bicarbonate solution (6 x 100 mL), brine (2 x 100 mL) and dried over $MgSO_4$. Evaporation gave a mixture containing



(2.5 g, 36%) as a brown oil.

Following the procedure in Example 480 the above sulfonyl chloride (2.5 g, 9.3 mmol) was reacted with Example 36 Part D amine (0.62 g, 1.2 mmol) followed by treatment with HCl to give title compound (210 mg, 26%) as a white solid.

m.p. 142-146°C

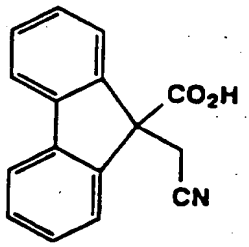
MS (ES, + ions): 678 (M + H)

Anal. Calc. for $C_{37}H_{39}ClF_3N_3SO_4$ + 0.4 H_2O:
C, 61.60; H, 5.56; N, 5.82; Cl, 4.91;
S, 4.44; F, 7.90.
Found: C, 61.67; H, 5.55; N, 5.62; Cl, 4.66;
S, 4.31; F, 7.95.

Example 177

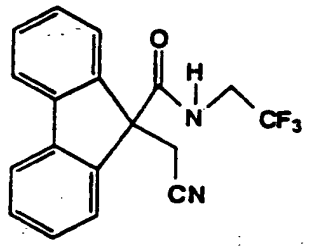
[1-[[[2-[9-[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl]amino]carbonyl]-4-piperidinyl]carbamic acid, 1,1-dimethylethyl ester

A.



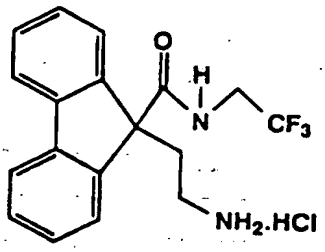
To a solution of 9-fluorenecarboxylic acid (10.5 g, 50 mmol) in THF (500 mL) at 0°C was added dropwise a solution of n-butyllithium (44 mL of a 2.5 M solution in hexanes, 110 mmol,) over 15 min under argon. The dark yellow solution was stirred at 0°C for 30 min, and then chloroacetonitrile (3.8 mL, 60 mmol) was added dropwise over 3 min. The dark orange reaction mixture was stirred at 0°C for 10 min, warmed to room temperature and stirred for 3h. The reaction mixture was diluted with H_2O (250 mL) and Et_2O (250 mL), and concentrated *in vacuo* to 300 mL. Water (200 mL) and CH_2Cl_2 (500 mL) were added. The mixture was acidified to pH 1.85 with 1N HCl and extracted with CH_2Cl_2 (6 x 250 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give crude solid title compound (10.45 g, 76.7%).

B.



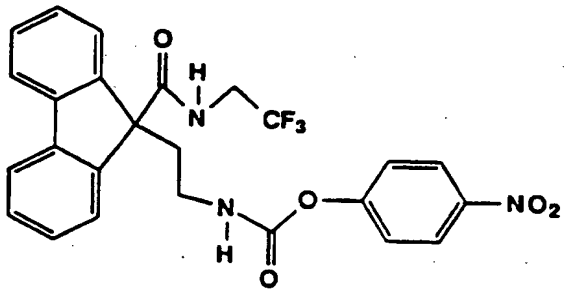
To a solution of Part A compound (6.7 g, 26.9 mmol, dried by concentration with THF/toluene) and DMF (102 µl, 1.36 mmol) in CH_2Cl_2 (80 mL) under N_2 was added oxalyl chloride (20.5 mL of a 2.0M solution in CH_2Cl_2, 40.6 mmol). The reaction was stirred at room temperature for 1.5 h and concentrated *in vacuo* and then dried under high vacuum to give the crude acid chloride. Triethylamine (11.3 mL, 81.0 mmol) was added to a suspension of 2,2,2-trifluoroethylamine hydrochloride (4.38 g, 32.4 mmol) in CH_2Cl_2 (50 mL) at 0°C under N_2. The resulting thick slurry was stirred at 0°C for 5 min and then a solution of the crude acid chloride in CH_2Cl_2 (30 mL) was added dropwise over 5 min. The reaction mixture was stirred at 0°C for 10 min. Dichloromethane (100 mL) was added and the solution was washed with 1N HCl (2 x 80 mL) and saturated $NaHCO_3$ (80 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give foamy solid 8.3 g. This material was combined with another batch of crude solid (4.4 g) and the combined mixture was purified by flash chromatography on silica gel (1200 mL), eluting with CH_2Cl_2, to give title compound (10.5 g, 83.3 %) as a solid.

C.



A solution of Part B compound (4.5 g, 13.6 mmol) in absolute ethanol (400mL)/$CHCl_3$ (7 mL) was hydrogenated at 50 psi over 10% Pd/C (2.1 g) for 3 days. The catalyst was removed by filtration through a nylon 66 filter, and the filtrate was concentrated *in vacuo* to give crude solid title compound (4.8 g).

D.



To a solution of the crude Part C compound (4.0 g) in THF (80 mL) and pyridine (3.5 mL, 43.4 mmol) at room temperature was added a solution of 4-nitrophenyl chloroformate (1.46 g, 7.22 mmol) in THF (25 mL). The mixture was stirred at room temperature overnight, concentrated in *vacuo* to remove THF, and diluted with EtOAc (700 mL). The EtOAc was washed with 5% $NaHCO_3$ (4 x 50 mL), H_2O (4 x 50 mL), 0.2N HCl (5 x 50 mL), H_2O (2 x 40 mL), and brine (40mL) and then dried over Na_2SO_4. Evaporation gave 3.1 g of a foam, which was purified by flash chromatography on

silica gel (500 mL), eluting with EtOAc/hexane (20:80 to 35:75) to give title compound (1.59 g, 41.6 %) as pale yellow solid (mp 138-140°C).

E. [1-[[[2-[9-[[(2,2,2-Trifluoroethyl)-amino)carbonyl]-9H-fluoren-9-yl]ethyl]-amino]carbonyl]-4-piperidinyl]carbamic acid, 1,1-dimethylethyl ester

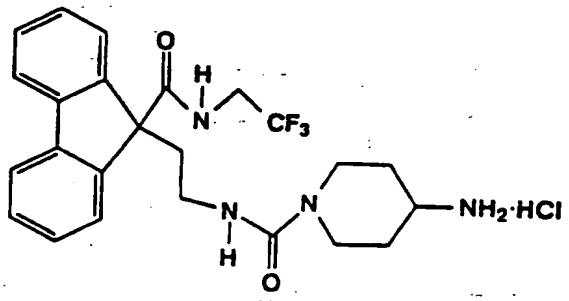
To a solution of Part D compound (1.59 g, 3.18 mmol) in CH_2Cl_2 (30 mL) under N_2 was added a solution of Example 10 Part B ester (1.27 g, 6.36 mmol) in CH_2Cl_2 (20 mL), followed by 4-dimethylaminopyridine (56 mg, 0.46 mmol). After stirring overnight at room temperature, the reaction mixture was diluted with CH_2Cl_2 (50 mL), washed with 0.1 N NaOH (3 x 40 ml), H_2O (2 x 40 mL), 1% $KHSO_4$ (2 x 40 ml), H_2O (40 mL), 5% $NaHCO_3$ (2 x 40 mL), H_2O (40 mL) and brine 40 mL) and then dried over Na_2SO_4. Evaporation of the CH_2Cl_2 gave 1.8 g of a foam, which was purified by flash chromatography on silica gel (100 mL), eluting with EtOAc/hexane (60:40 to 100:0), to give title compound (1.43 g, 80.1%) as a white solid. mp 77-80°C.

MS (ESI, + ions) m/z 561 (M + H), 1121 (2M + H); (-ion) 559 (M - H).
Anal. Calcd for $C_{29}H_{35}N_4O_4F_3$ + 0.15CH_2Cl_2 + 0.4$CH_3CO_2C_2H_5$:
C, 60.69; H, 6.38; N, 9.21; F, 9.36
Found C, 60.83; H, 6.36; N, 9.29; F, 9.61.

Example 178

9-[2-[[[4-(Benzoylamino)-1-piperidinyl]carbonyl]-amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide

A.



To a solution of Example 177 compound (1.1 g, 1.97 mmol) in THF (4 mL) was added 4N HCl in dioxane (9 mL, 36.4 mmol). The reaction mixture was stirred at room temperature for 3 h and concentrated in vacuo and then from dioxane (3 x 10 mL) to give crude title compound (1.46 g) as a white foamy solid.

B. 9-[2-[[[4-(Benzoylamino)-1-piperidinyl]-carbonyl]amino]ethyl]-N-(2,2,2-trifluoro-ethyl)-9H-fluorene-9-carboxamide

To a solution of crude Part A compound (730 mg, 0.98 mmol) and triethylamine (615 µL, 4.41 mmol) in CH_2Cl_2 (10 mL) at 0°C was added dropwise benzoyl chloride (172 µL, 1.47 mmol). The reaction was stirred at 0°C for 30 minutes and diluted with CH_2Cl_2 (30 mL). The solution was washed with 0.1N NaOH (2 x 40 mL), H_2O (40 mL), 0.2N HCl (2 x 40 mL), H_2O (40 mL) and brine (40 ml), then dried over $MgSO_4$ and concentrated to a white solid (1.6 g). Purification of this solid over silica gel (100 mL) by eluting with 5% methanol in dichloromethane gave title comopund (427 mg, 77.2%) as white solid.

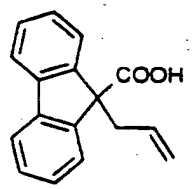
m.p. 220-222°C.
MS (ESI, + ions) m/z 565 (M + H), 582 (M + NH_4); (-ion) 563 (M - H).

Anal. Calcd For $C_{31}H_{31}N_4O_3F_3$:
C, 65.95; H, 5.53; N, 9.92; F, 10.09.
Found: C, 65.80; H, 5.41; N, 9.84; F, 9.98.

Example 179

4-[[(1,1-Dimethylethoxy)carbonyl]amino]-1-piperidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl ester

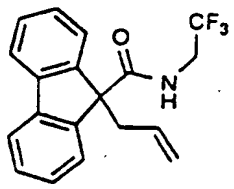
A.



To a stirred solution of 8.41 g (40 mmol) of 9-fluorenecarboxylic acid in 400 mL of dry THF at 0°C under argon was added, over 15 min, 35.2 mL of 2.5 M n-butyllithium in hexane (88 mmol). The reaction was stirred at 0°C for 30 min and then 4.2 mL (48.5 mmol) of allyl bromide was added over 15 min. The reaction was stirred at 0°C for 15 min and at room temperature for 1 h and then quenched by addition of water (80 mL). The THF was removed *in vacuo* and the aqueous mixture was extracted with ether (2 x 100 mL). The aqueous layer was layered with CH_2Cl_2 (150 mL) and then acidified with 1N HCl (pH < 2). After extraction, the aqueous was extracted with additional CH_2Cl_2 (2 x 100 mL), and the combined CH_2Cl_2 extracts were washed with water, dried ($MgSO_4$) and

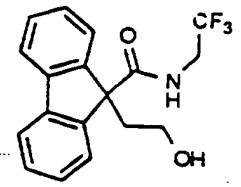
concentrated to give 9.41 g (94%) of title compound as an amorphous solid.

B.

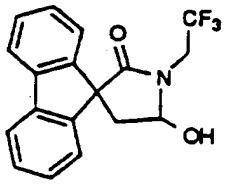


Part A compound (9.30 g) was dried by concentration *in vacuo* from a mixture of dry THF and dry toluene (2x). To a stirred solution of this acid in 100 mL of dry CH_2Cl_2 and 143 mL of DMF under nitrogen was added cautiously 28 mL of 2.0 M oxalyl chloride in CH_2Cl_2 (55.8 mmol). The reaction was stirred at room temperature for 1.5 h and concentrated *in vacuo* and then dried at 0.5 mm for 1 h to give the crude acid chloride of Part A acid. Triethylamine (15.6 mL, 112 mmol) was added to a stirred suspension of 6.04 g (44.6 mmol) of 2,2,2-trifluoroethylamine hydrochloride in 75 mL of dry CH_2Cl_2 at 0°C under argon. The slurry was stirred at 0°C for 10 min and then a solution of the crude acid chloride in 35 mL of CH_2Cl_2 was added over 10 min keeping the internal temperature <12°C. The reaction was stirred at 0°C for 15 min and at room temperature for 1 h and then diluted with 150 mL of CH_2Cl_2. The CH_2Cl_2 was washed with 1N HCl (2 x 75 mL), water (180 mL), 5% $NaHCO_3$ (120 mL), and water (2 x 180 mL), dried (Na_2SO_4), and concentrated to a residue (12.67 g). Chromatography of this residue over 500 g of silica gel provided 10.74 g (87%) of title compound as an amorphous white solid, mp 84-86°C.

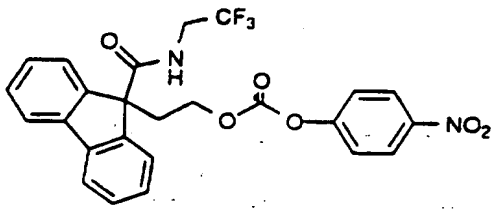
C.



Ozone (in oxygen) was passed into a stirred solution of 5.30 g of Part B compound in 80 mL of dry CH_3OH at -55°C for 1 h. Nitrogen was bubbled through the reaction for 10 min at -55°C and then the reaction was warmed to -30°C. A solution of $NaBH_4$ (908 mg, 24 mmol) in 20 mL of 50% aqueous CH_3OH cooled to 0°C was added and the reaction was stirred at -30°C for 70 min. The cooling bath was removed, the pH was adjusted to < pH 2 (3N HCl), and the reaction was concentrated to remove CH_3OH. The residue was partitioned between EtOAc and water, and the EtOAc was washed with water (4 x), dried (Na_2SO_4), and concentrated to a residue (6.67 g). Chromatography of this residue over 475 g of silica gel using hexane-EtOAc (6:4) and then hexane-EtOAc (1:1) afforded 2.77 g (49%) of title compound as an amorphous solid. An earlier eluting fraction provided 1.97 g of compound



D.



4-Nitrophenyl chloroformate (1.2 g, 6 mmol) was added to a stirred solution of 1.34 g (4 mmol) of Part C compound and 0.97 mL (12 mmol) of dry pyridine in 15 mL of dry CH_2Cl_2 at room temperature under argon. The reaction was stirred for 20 min at room temperature and then diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% $NaHCO_3$ (4x), water, dilute HCl (2x), and water (3x), dried (Na_2SO_4), and concentrated to give crude title compound in the form of a foamy residue (2.30 g).

E. 4-[[(1,1-Dimethylethoxy)carbonyl]amino]-1-piperidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl ester

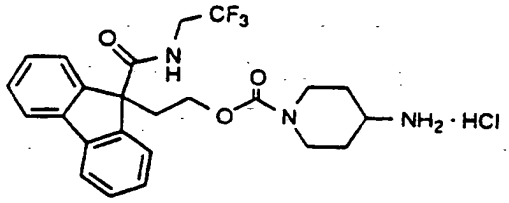
4-Boc-aminopiperidine (1.58 g, 7.90 mmoL) was added to a stirred solution of 2.29 g of the above preparation of Part D compound in 30 mL of dry CH_2Cl_2 at room temperature under argon. The reaction was stirred at room temperature for 2 h and then diluted with CH_2Cl_2. The CH_2Cl_2 solution was washed with dilute NaOH (2x), water (2x), dilute $KHSO_4$ (2x), and water (3x), dried (Na_2SO_4), and concentrated to give 2.63 g of an oily residue. Chromatography of this residue over 230 g of silica gel using hexane-EtOAc (6:4) and subsequent crystallization from EtOAc-hexane provided 2.07 g (94%) of title compound as a white solid having mp 120-122°C.

Anal. Calcd for $C_{29}H_{34}F_3N_3O_5$ + 0.5 $CH_3CO_2C_2H_5$:
C, 61.48; H, 6.32; N, 6.94; F, 9.41
Found: C, 61.25; H, 6.39; N, 6.85; F, 9.42.
MS (ESI-NH_3, + ions) 562 (M+H), 579 ($M+NH_4$);
(- ions) 560.

Example 180

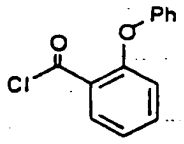
4-[(2-Phenoxybenzoyl)amino]-1-piperidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl ester

A.



To a solution of 898 mg (1.6 mmol) of Example 179 compound in 3 mL of dry THF under argon at room temperature was added 6 mL of 4N HCl in dioxane (24 mmol). The reaction was stirred at room temperature for 2 h and then stored overnight at 5°C. The reaction was concentrated *in vacuo* and then concentrated from dry dioxane (2 x 5 mL) and then dried at 0.5 mm for 2h to afford crude title compound as an amorphous residue.

B.



To 428 mg (2.0 mmol) of 2-phenoxybenzoic acid and 10 µL of DMF in 4 mL of dry CH_2Cl_2 at 0°C under nitrogen was added 1.5 mL of 2.0 M oxalyl chloride in

CH_2Cl_2 (3.0 mmoL). The reaction was stirred at room temperature for 1.5 h and concentrated *in vacuo* and then dried at 0.5 mm for 1 h to give the crude title acid chloride as a pale yellow oil. This oil was dissolved in 3.2 mL of CH_2Cl_2.

C. 4-[(2-Phenoxybenzoyl)amino]-1-piperidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl ester

To a stirred solution of one-half of the crude preparation of Part A compound above (ca. 0.8 mmoL) in 4 mL of dry CH_2Cl_2 at 0°C under argon was added 0.46 mL (4 mmol) of triethylamine. The solution was stirred at 0°C for 5 min and then a 2.0 mL aliquot of the above solution of Part B compound in 3.2 mL of CH_2Cl_2 (ca. 1.2 mmoL of crude Part B compound) was added. The reaction was stirred at 0°C for 2.5 h and then diluted with CH_2Cl_2. The CH_2Cl_2 was washed with dilute NaOH (2x), water (2x), dilute HCl (2x), and water (3x), dried (Na_2SO_4), and concentrated to a thick oil (577 mg). Chromatography of this oil over 45 g of silica gel using hexane-EtOAc (1:1) provided 414 mg of title compound (79%) as a foam having mp 68-73°C.

Anal. Calcd for $C_{37}H_{34}F_3N_3O_5$ + 0.2 $CH_3CO_2C_2H_5$:
C, 67.23; H, 5.31; N, 6.22; F, 8.44
Found: C, 67.04; H, 5.20; N, 6.18; F, 8.70.

MS (ESI-NH_3, + ions) 658 (M+H), 675 ($M+NH_4$).

Example 181

9-[4-[4-[(2-Phenoxybenzoyl)amino]-1-piperidinyl]-pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

A solution of Example 175 compound (1.25 g, 2.23 mmol) in 10 mL of 4 N hydrogen chloride in dioxane was stirred, protected by a calcium chloride drying tube, for 3 h. The solution was evaporated at 30°C and the resulting solid was re-dissolved to a total volume of 20.0 mL with dichloromethane. To 10.0 mL of this stirred solution (*ca.* 1.12 mmol), cooled to -10°C under argon, was added triethylamine (0.4 mL, 2.9 mmol) and then the 2-phenoxybenzoyl chloride (320 mg, 1.38 mmol) solution in 10 mL of dichloromethane over 10 min. After 1 h, the reaction was quenched with saturated sodium bicarbonate solution and extracted twice with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated. Purfication by flash chromatography (5 x 20 cm column, ethyl acetate as elutant) provided a colorless oil, 603 mg, 77%. The oil was dissolved in 5 mL of ethyl acetate and then 0.25 mL of 4 N HCl in dioxane was added. Ether was added until a gummy precipitate formed. Decanting and drying *in vacuo* gave title compound as a white solid, 650 mg, mp 136-138°C.

Anal. Calcd for $C_{39}H_{40}F_3N_3O_3+HCl+H_2O$:
C, 65.95; H, 6.10; Cl, 4.99; F, 8.02;
N, 5.92

Found: C, 65.87; H, 6.08; Cl, 5.13; F, 7.96; N, 5.92.
MS (electrospray, + ions) m/e 654 (M + H).

Examples 182 to 187

Following the procedures set out herein-before and in the working Examples, the following additional compounds were prepared.

Example 182
9-[2-[[[4-[(2-Phenoxybenzoyl)amino]-1-piperidinyl]carbonyl]amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide.

MS (ESI, + ion): 657 (M+H)
Anal. Calcd for $C_{37}H_{35}N_4O_4F_3$+0.2 CH_2Cl_2+0.1 $CH_3CO_2C_2H_5$: C, 66.17; H, 5.35; N, 8.21; F, 8.35
Found: C, 66.14; H, 5.29; N, 8.13; F, 8.47.
mp 84-87°C.

Example 183
4-(Benzoylamino)-1-piperidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl ester.

MS (ESI-NH_3, + ions) 566 (M+H)
Anal. Calcd for $C_{31}H_{30}F_3N_3O_4$+0.2 $CH_3CO_2C_2H_5$+0.25 H_2O: C, 64.99; H, 5.51; N, 7.04; F, 9.70
Found: C, 64.77; H, 5.45; N, 7.15; F, 10.10.
mp 75-85°C.

Example 184
9-[4-[4-(Benzoylamino)-1-piperidinyl]pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

MS (electrospray, + ions) m/z 564 (M+H)
Anal. Calcd for $C_{33}H_{36}F_3N_3O_2$ + HCl + H_2O:

C, 64.12; H, 6.36; Cl, 5.74; F, 9.22;
N, 6,80
Found: C, 64.17; H, 6.27; Cl, 5.65; F, 9.65;
N, 6.60.
mp 130-132°C.

Example 185

9-[4-[4-[[(1,1-Dimethylethoxy)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide.

mp 76-79°C.
MS (ES, + ions, NH_3) m/z 578 (M+H).

Example 186

9-[4-[4-(Benzoylamino)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide.

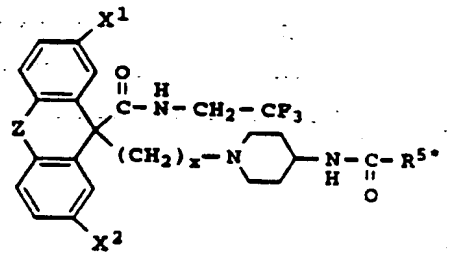
mp 167-169°C.
MS (ES, + ions, NH_3) m/z 582 (M+H).

Example 187

9-[4-[4-[[(2-Phenoxyphenyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide.

mp 164-166°C.
MS (ES, + ions, NH_3) m/z 674 (M+H).

In accordance with the present invention, another class of preferred compounds is provided which are inhibitors of MTP and have the structure I*



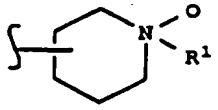
wherein Z is a bond, O or S;

X^1 and X^2 are independently H or halo, preferably F;

x is an integer from 2 to 6, preferably from 3 to 5, and $(CH_2)_x$ may be optionally substituted with 1, 2 or 3 substituents which are the same or different and are alkyl or halo; and

R^{5*} is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each R^{5*} group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different as defined hereinafter; and

including piperidine N-oxides of the formula I compound, that is

 ; and

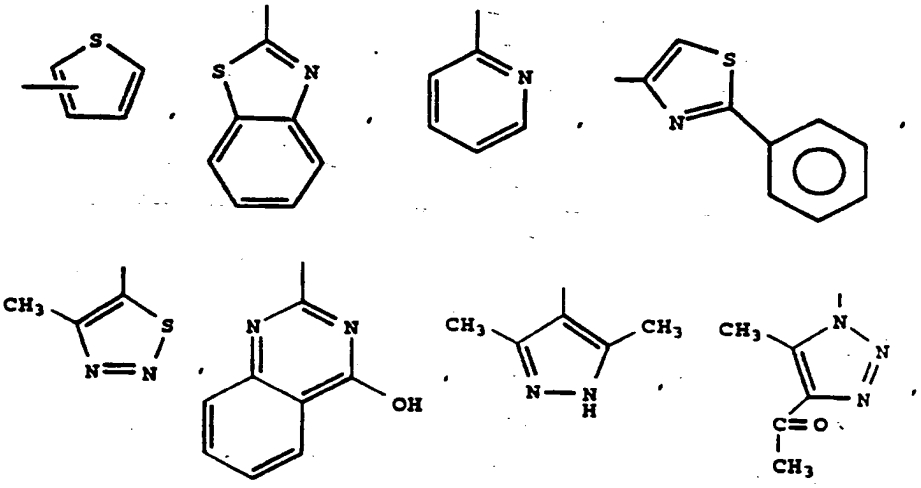
including pharmaceutically acceptable salts thereof such as alkali metal salts such as lithium sodium or potassium, alkaline earth metal salts such as calcium or magnesium, as well as zinc or aluminum and other cations such as ammonium, choline, diethanolamine, ethylenediamine, t-butyl-amine, t-octylamine, dehydroabietylamine, as well as pharmaceutically acceptable anions such as chloride, bromide, iodide, tartrate, acetate, methanesulfonate,

maleate, succinate, glutarate, and salts of naturally occurring amino acids such as arginine, lysine, alanine and the like, and prodrug esters thereof.

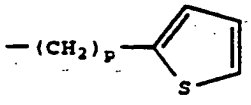
The R^{5*} group may be substituted with 1, 2, 3 or 4 substituents, including

(1) halogen such as Cl, F, CF_3, and I,

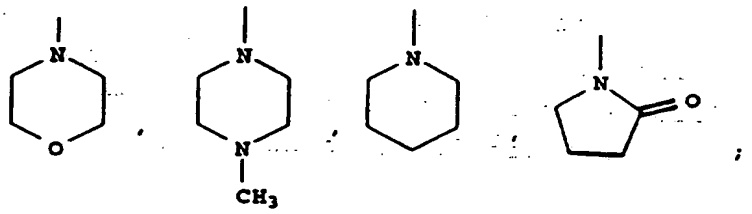
(2) heteroaryl, including monocyclic or bicyclic ring systems, which includes 1, 2 or 3 heteroatoms which are S, N and/or O, and which includes from 2 to 10 carbons in the ring or ring system, such as



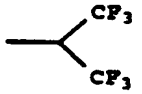
;

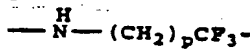
(3) heteroarylalkyl wherein heteroaryl is as defined above such as  ;

(4) cycloheteroalkyl which includes 1, 2 or 3 hetero atoms which are N, S or O in a monocyclic or bicyclic ring system such as

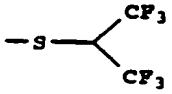
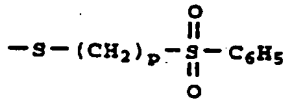


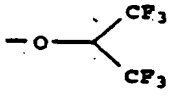
(5) alkyl;

(6) aryl such as phenyl, phenyl substituted with (a) halo, (b) alkyl, (c) CF_3O, (d) alkoxy (e)  , (f) CF_3, or (g) phenyl;

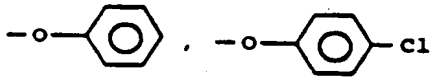
(7) alkylamino such as  ;

(8) alkyl(aryl)amino such as $-N(CH_3)C_6H_5$;

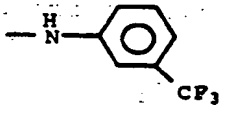
(9) alkythio such as $-S-(CH_2)pCF_3$,  ,  , -S-alkyl, ;

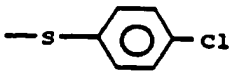
(10) alkoxy such as $-O-(CH_2)p-CF_3$,  , OCH_3;

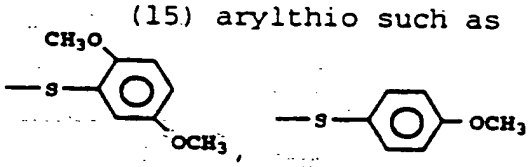
(11) cycloalkyl such as cyclohexyl;

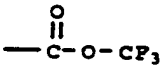
(12) aryloxy such as  ;

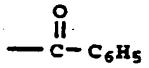
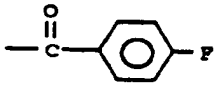
(13) amino;

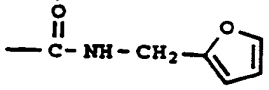
(14) arylamino such as  ;

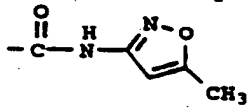
(15) arylthio such as  ,

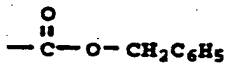
 ;

(16) acyl such as (a) alkanoyl, such as  , (b) alkoxycarbonyl, such as  ,

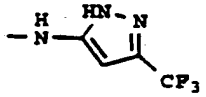
(c) aroyl, such as  ,  ,

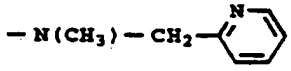
(d) heteroarylaminocarbonyl, such as  ,

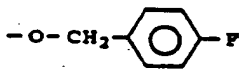
 , (e) arylalkyloxycarbonyl, such as

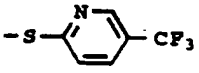
 ;

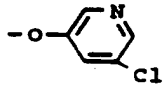
(17) arylthioalkyl, such as $-CH_2-S-C_6H_5$;

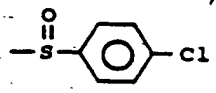
(18) heteroarylamino, such as  ,

 ;

(19) arylalkyloxy, such as  ;

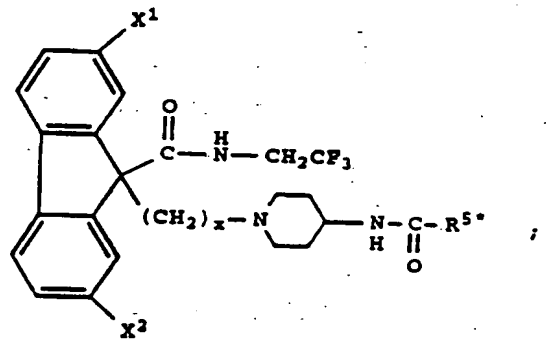
(20) heteroarylthio, such as  ;

(21) heteroaryloxy, such as  ; and

(22) arylsulfinyl, such as  .

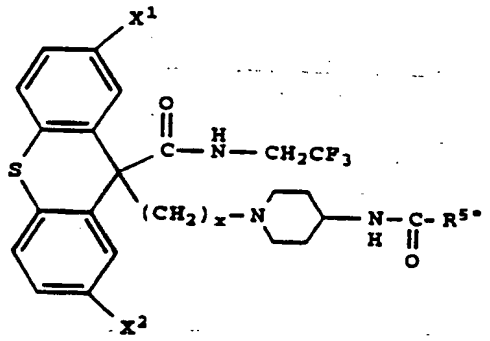
Thus, the compounds of formula I* of the invention encompass compounds of the structure

I^{a*}



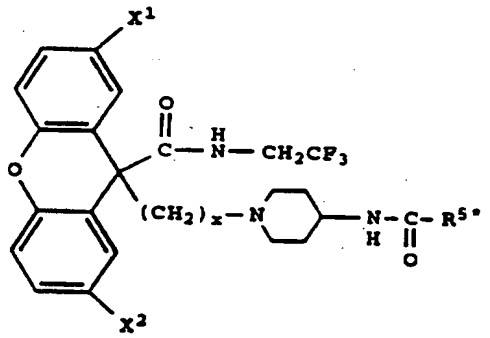
;

I^{b*}



; and

I^{c*}

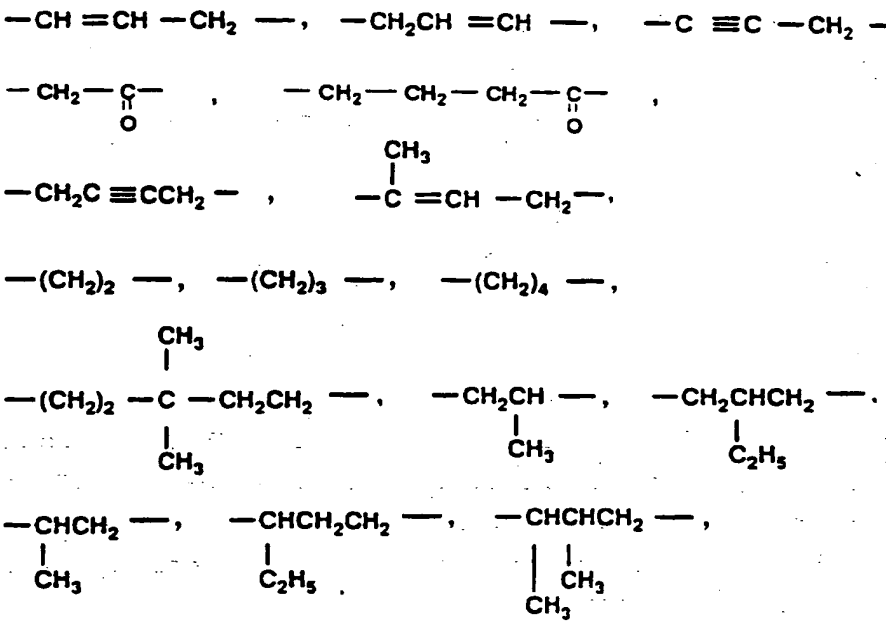


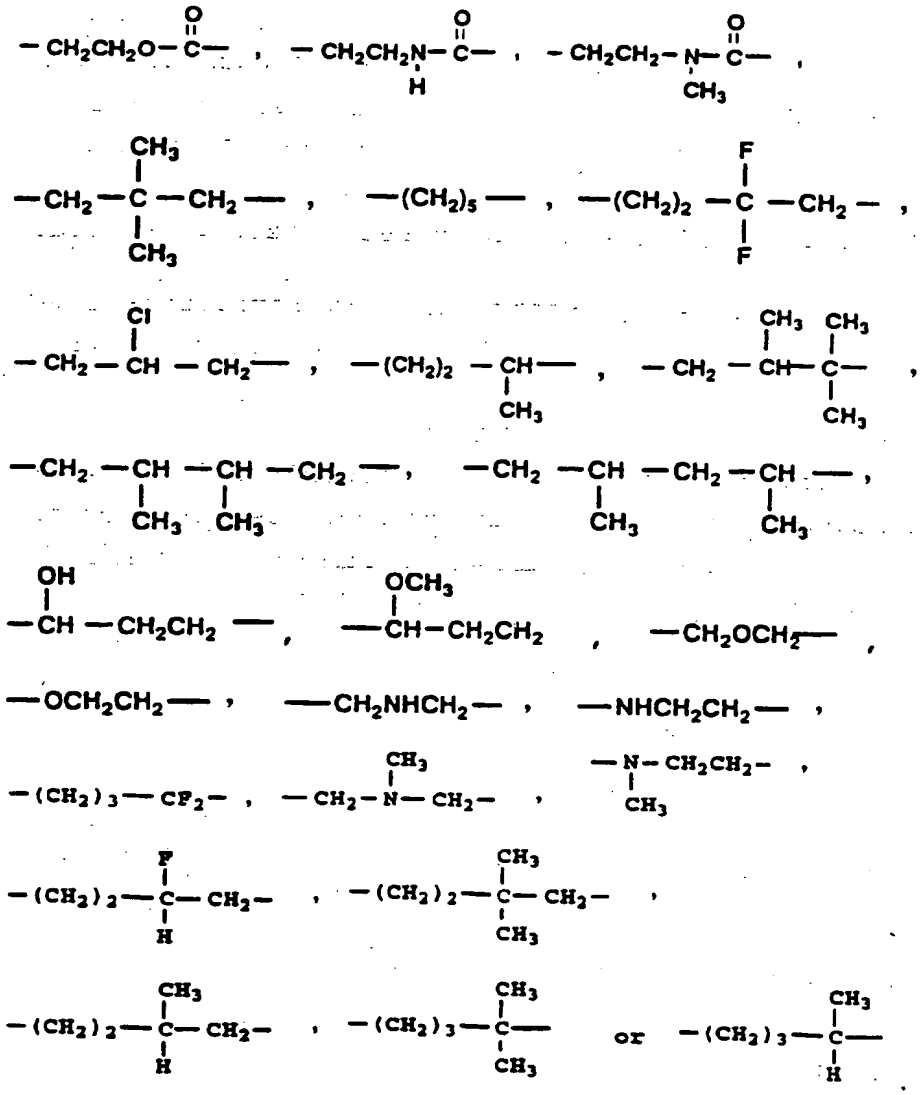
In addition, in accordance with the present invention, a method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity is provided, wherein a compound of formula I* as defined hereinbefore is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

Furthermore, in accordance with the present invention, a method is provided for lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, wherein a compound of formula I* as defined hereinbefore is administered in an amount which decreases the activity of microsomal triglyceride transfer protein.

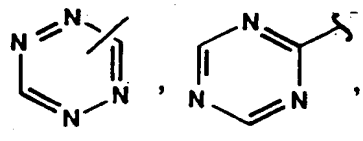
Suitable $(CH_2)_x$ groups (were x is 2 to 6, preferably 3 to 5) (which may include alkylene, alkenylene or alkynylene groups) as defined herein, may optionally include 1, 2, or 3 alkyl or halogen and in addition, may have one of the carbon atoms in the chain replaced with an oxygen atom, N-H, N-alkyl or N-aryl.

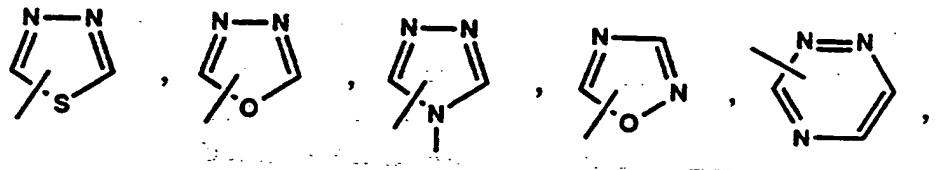
Examples of $(CH_2)_x$ groups include





The term "heteroaryl" as used herein alone or as part of another group is defined above. Additional examples of "heteroaryl" groups are set out below.



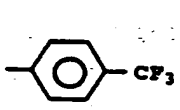
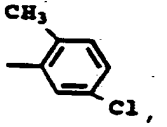


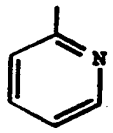
and the like, and includes all possible N-oxide derivatives.

Preferred are compounds of formula I* where Z is a bond;

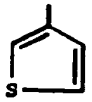
X^1 and X^2 are H;

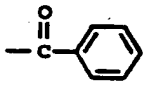
R^{5*} is aryl such as phenyl substituted with

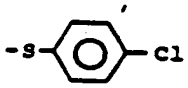
(1) aryl such as phenyl,   ,

(2) heteroaryl such as   ,

(3) halo such as Cl

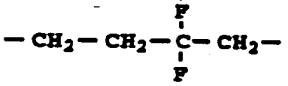
R^{5*} is heteroaryl such as  or  substituted with

(1) aroyl such as  ,

(2) arylthio such as 

wherein the R^{5*} substituent is preferably in the position adjacent to the carbon linked to  .

$(CH_2)_x$ is $-(CH_2)_4-$ or

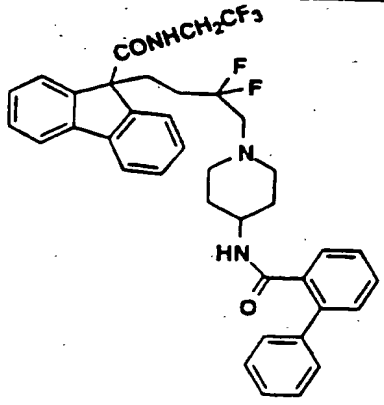


The following Examples represent additional preferred embodiments of the invention. All temperatures are in °C unless indicated otherwise.

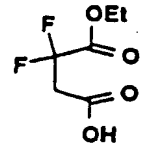
NOTE: The phrase "flash chromatography" as employed in the following examples refers to chromatography performed on EM Industries Silica Gel 60, 230-400 mesh under 10-20 psi of nitrogen pressure.

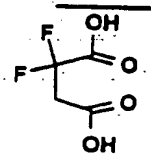
Example 1*

9-[4-[4-[([1,1-Biphenyl]-4-ylcarbonyl)amino]-1-piperidinyl]-3,3-difluorobutyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride



A.

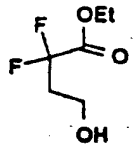




A mixture of (5.18 g, 33.6 mmol), acetyl chloride (5.2 mL) and acetic anhydride (5.2 mL) was heated to 50°C under argon for 1 h. The

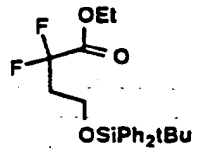
reaction was cooled and evaporated. The residue was dissolved in EtOH (20 mL) and stirred at room temperature (RT) under argon. After 16 h, the solution was evaporated, the residue redissolved in Et_2O and the solution dried (Na_2SO_4) to give title compound as a colorless oil, 5.91 g, 97% material balance. The compound was used without further purification.

B.



To a stirred solution of Part A compound (1.82 g, 10.0 mmol) in THF (10 mL) at room temperature under argon was added a solution of borane-methyl sulfide complex (1.25 mL, 13.2 mmol) in dichloromethane (14 mL). The reaction was set to reflux. After 24 h, the reaction was cooled, methanol (20 mL) was added and the reaction again set to reflux. After 1 h, the excess solvents were distilled at atmospheric pressure. The residue was bulb-to-bulb distilled at reduced pressure to provide title compound as a colorless oil, 1.45 g, 86%.

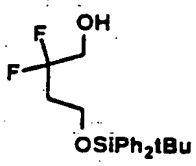
C.



To a stirred solution of Part B compound (1.40 g, 8.33 mmol) in DMF (10 mL) at room temperature under argon was added $Ph_2tBuSiCl$ (2.6 mL, 9.2 mmol)

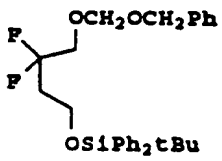
and imidazole (1.4 g, 21 mmol). After 2 h, the reaction was quenched with water and extracted three times with ether. The organic extracts were combined, dried (Na_2SO_4) and evaporated to give a brown oil. Purification by flash chromatography on silica gel (5 x 20 cm column, 2:7 dichloromethane/hexanes) gave title compound as a colorless oil, 1.83 g, 54%.

D.



To a stirred solution of Part C compound (1.73 g, 4.26 mmol) in THF (5 mL) at room temperature under argon was added lithium borohydride solution (1.2 mL, 2.4 mmol, 2 M in THF). After 16 h, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted three times with EtOAc. The organic extracts were dried (Na_2SO_4) and evaporated to give title compound as a colorless oil, 1.51 g, 97%. The compound was used in subsequent reactions without further purification.

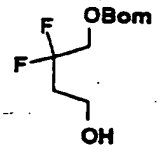
E.



To a stirred solution of Part D compound (1.50 g, 4.12 mmol) in diisopropylethylamine (5 mL) at 10°C under argon was added benzyloxymethyl chloride (BomCl) (0.7 mL, 4.9 mmol) in one portion. A

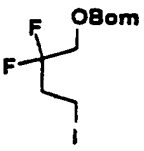
precipitate began to form within 10 min. After 1 h, hexane was added to the reaction mixture and the resulting slurry washed with 10% hydrochloric acid (20 mL) and once with water. The organic layer was dried ($MgSO_4$) and evaporated to give a light yellow oil. Purification by flash chromatography on silica gel (5 x 20 cm column, 2:3 dichloromethane/hexane) gave title compound as a colorless oil, 1.77 g, 89%.

F.



To a stirred solution of Part E compound (1.72 g, 3.55 mmol) in THF (5 mL) at room temperature under argon was added tetrabutylammonium fluoride solution (TBAF, 7.5 mL, 7.5 mmol, 1 M in THF). After 1 h, the reaction was quenched with brine and extracted twice with EtOAc. The combined extracts were dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (5 x 12 cm column, 1:9 EtOAc/dichloromethane) provided title compound as a colorless oil, 774 mg, 89%.

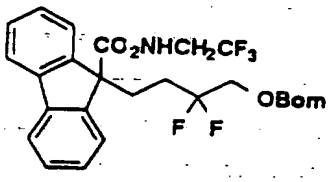
G.



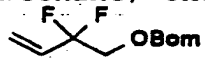
To a stirred solution of Part F compound (770 mg, 3.13 mmol), triphenylphosphine (826 mg, 3.15 mmol) and imidazole (470 mg, 6.9 mmol) in THF (10 mL) at room temperature under argon was added a solution

of iodine (800 mg, 3.15 mmol) in THF (5 mL) dropwise over 10 min. The reaction mixture was diluted with ether and washed once with saturated sodium bicarbonate (containing 5% $NaHSO_3$). The organic extract was dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (5 x 10 cm column, dichloromethane) provided title compound as a colorless oil, 935 mg, 84%.

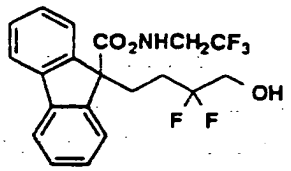
H.



To a solution of 9-fluorenecarboxylic acid (631 mg, 3.0 mmol) in THF (5 mL) under argon at -10°C was added a solution of sodium bis(trimethylsilyl)-amide (6.2 mL, 6.2 mmol, 1 M in THF) over 10 min. The resulting slurry was stirred 60 min and then a solution of Part G compound (930 mg, 2.61 mmol) in THF (5 mL) was added. The reaction was allowed to warm to room temperature and stirred. After 48 h, the reaction was quenched with 10% citric acid solution and extracted twice with EtOAc. The organic extracts were combined, dried ($MgSO_4$) and evaporated. The oily residue was dissolved in dichloromethane (10 mL) and treated, at room temperature, with oxalyl chloride (0.52 mL, 6.0 mmol) and DMF (0.1 mL). After 1 h, the reaction was evaporated and then redissolved in dichloromethane (5 mL). This solution was added, dropwise over 10 min, to a stirred slurry of trifluoroethylamine hydrochloride (502 mg, 3.70 mmol) and Et_3N (1.12 mL, 8 mmol) in dichloromethane (10 mL) at 0°C under argon. After 1 h, the reaction was

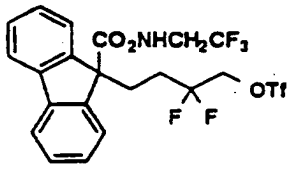
quenched with 10% citric acid solution and extracted twice with EtOAc. The organic extgracts were combined, dried ($MgSO_4$) and evaporated. Purification by flash chromatography (5 x 20 cm column, 1 L dichloromethane, then 5:95 ether/dichloromethane) to provide  , 375 mg, 47% and then title compound, 120 mg, 9% as colorless oils.

I.



A stirred slurry of Part H compound (108 mg, 0.208 mmol) and 20% Pd(OH)$_2$-on-carbon (200 mg) in cyclohexene (2 mL) and ethanol (5 mL) was refluxed for 2 h under argon. The reaction was cooled, evaporated, diluted with EtOAc, dried ($MgSO_4$) and filtered through a 0.75 m nylon filter. Evaporation provided title compound as a colorless oil, 53 mg, 64%.

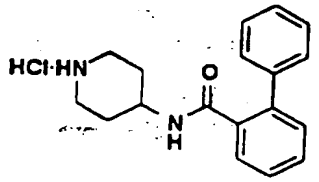
J.



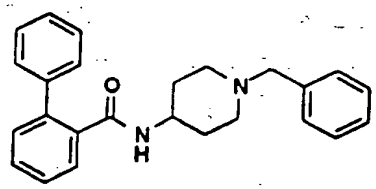
To a solution of Part I compound (50.9 mg, 0.128 mmol) and pyridine (68 mL, 0.8 mmol) in dichloromethane (1 mL) at 0°C under argon was added triflic anhydride (40 mL, 0.15 mmol) over 2 min. After 1 h, the reaction was quenched with 1 M

hydrochloric acid and extracted twice with EtOAc. The organic extracts were combined, dried ($MgSO_4$) and evaporated to give title compound as an orange crystalline solid, 68 mg, 100%.

K.

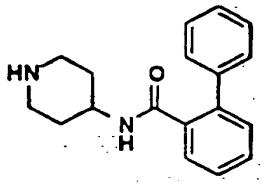


K(1).



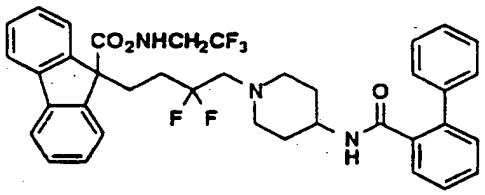
To a solution of 2-biphenyl carboxylic acid (31.2 g, 160 mmol) in methylene chloride (300 ml) was added the oxalyl chloride (21 ml, 280 mmol), followed by a few drops of DMF. The reaction bubbled vigorously and was stirred under argon at room temp 2h. The solvent was evaporated in vacuo at less than 25°C, and the residue was dissolved in methylene chloride (250 ml). This solution was added dropwise to a solution of 4-aminobenzyl piperidine (Aldrich, 25.0g, 130 mmol) and triethylamine (46 ml, 330 mmol) in methylene chloride (200 ml) at -5°C. The reaction stirred 30 minutes at that temperature after addition was complete. The reaction mixture was washed twice with water and once with brine. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo to give title compound as a light yellow solid (56.6 g, 95.4% yield).

K(2).



To a solution of Part K(1) compound (55.5 g, 150 mmol) in ethanol (500 ml) was added cyclohexene (167 ml, 1.6 mol) and 20% palladium hydroxide on carbon (11.1 g). The reaction was heated to reflux and stirred at that temperature 2.75 h. The warm reaction was filtered through Celite® and rinsed with ethanol and methanol. The filtrate was concentrated in vacuo to give a light yellow oil. This oil was triturated twice with ether to give a light yellow solid (30.1 g).

L.



To a stirred solution of Part J compound (68 mg.0.126 mmol) in toluene (2 mL) at room temperature under argon was added Part K compound (84 mg, 0.3 mmol) in DMF (0.5 mL). The solution was heated to 50°C. After 14 h, the reaction was cooled, diluted with ether and washed once with saturated sodium bicarbonate solution. The organic layer was dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (1 x 10 cm column, EtOAc) provided title compound as the free base as a

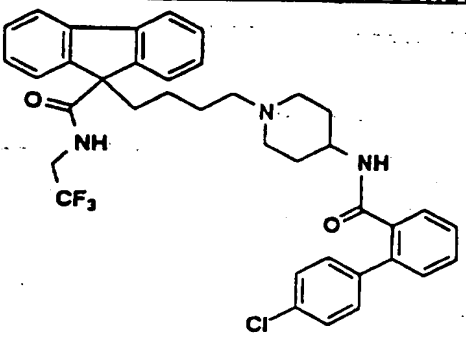
white foam, 57 mg, 68%. The foam was diluted with dichloromethane and 0.1 mL of 4 N hydrochloric acid. Evaporation provided the HCl salt of the title compound, 59 mg, mp 115-118°C.

TLC: R_f = 0.20 (free base, EtOAc, Silica gel 60)

Mass Spectrometry: (electrospray, + ions)
m/z 662 (M+H)

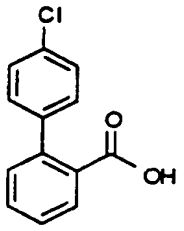
Example 2*

9-[4-[4-[[(4'-Chloro-[1,1'-biphenyl]-2-yl)carbonyl]-amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride



HCl salt

A.



The title compound was prepared by the method of Meyers by Grignard addition of p-chlorophenylmagnesium bromide to o-methoxy-phenyl-1,1-dimethyl-isoxazole and hydrolysis with 6 N HCl.

B. 9-[4-[4-[[(4'-Chloro-[1,1'-biphenyl]-2-yl)carbonyl]-amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

To a solution of the Part A acid (2.0 g, 8.6 mmol) in methylene chloride (35 ml) was added a 2 M solution of oxalyl chloride (6.0 ml, 12 mmol) in dichloromethane followed by a 2 drops of DMF. The reaction bubbled vigorously and stirred under argon at RT for 2h. The solvent was evaporated *in vacuo* at less than 25°C, and the residue was dissolved in THF (50 ml). This solution was added dropwise to a solution of the Example 11* Part C diamine (4.45 g, 8.6 mmol) and triethylamine (3.54 g, 35 mmol) in THF (150 ml) at 0°C. The reaction stirred in a melting ice bath 1h and warmed to RT and stirred for 48 h. The reaction mixture was diluted with ethyl acetate (200 mL) and washed once with water. The organic layer was dried ($MgSO_4$), and the solvent was removed *in vacuo* to give an off-white solid foam which was purified trituration with ethyl acetate to give a white solid.

The solid was diluted with ether (100 mL) and treated with 1M HCl in ether (10 mL, 10 mmol) in give a white powder which was filtered. The solid was collected and dried at 55°C (20 mm Hg) overnight to give 3.95 g (67%) of title compound as a white powder.

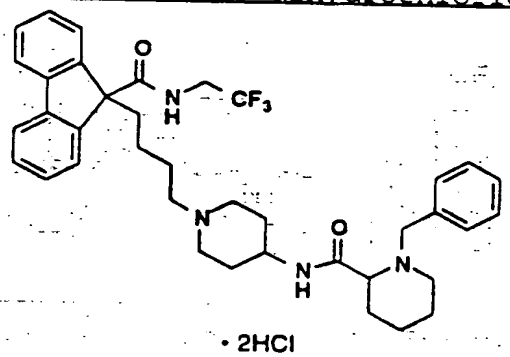
mp:140-150°C

MS (ES, + ions) m/z 660 (M + H); 1 Cl isotope pattern.

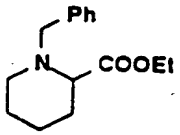
Anal Calcd. for $C_{38}H_{37}N_3O_2F_3Cl$ + HCl:
C, 63.07; H, 5.71; N, 5.81
Found: C, 62.79; H, 5.62; N, 6.05.

Example 3*

9-[4-[-4[[[1-(Phenylmethyl)-2-piperidinyl]carbonyl]-amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride



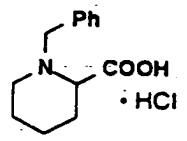
A.



Benzyl bromide (700ml, 5.7 mmol) was added dropwise to a slurry of ethyl pipecolinate hydrochloride (1.0 g, 5.2 mmol) and potassium carbonate (1.5 g, 11.4 mmol) in DMF (10 mL) under argon. The reaction was stirred at RT for 2.5 h., then the solvent was removed in vacuo. The residue was partitionated between dichloromethane (10 mL) and water (10 mL), and the aquous layer was extracted with dichloromethane (3 x 10 mL). The combined organic layers were dried over sodium sulfate, then concentrated in vacuo to give a cloudy oil, which was

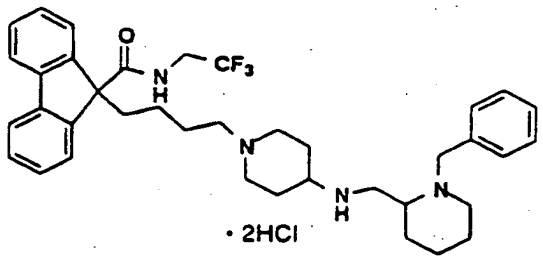
chromatographyed (10% ethyl acetate in hexane) on silica gel (60 g). Pure fractions were combined and evaporated to give title compound (1.24 g, 97%) as a colorless oil.

B.



A biphasic mixture of Part A compound (600 mg, 2.4 mmol) and 1N KOH (7.2 mL) in dioxane was stirred at RT overnight, then the reaction was heated at 50°C for 2 days. The reaction was cooled to RT then adjusted to pH 2 with 1N HCl. The cloudy mixture was concentrated in vacuo then pumped under high vaccum overnight. The solid product was stirred with chloroform (10 mL) for 15 min. then filtered. The filtrate was concentrated in vacuo to give title compound (411 mg, 67%) as a yellow foam.

C.



Ethyl 3-(3-dimethylamino)propyl carbodiimide (164 mg, 0.86 mmol) was added to a mixture of Example 11* Part C compound (404 mg, 0.78 mmol), Part B compound (200 mg, 0.78 mmol), hydroxybenzotriazole (105 mg, 0.78 mmol), and 4-methyl morpholine (300 ml,

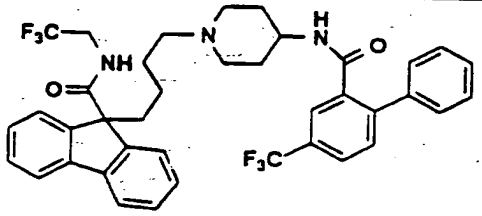
2.7 mmol) in dichloromethane (3 mL) under argon. The reaction was stirred at RT for 24 h., diluted with dichloromethane (20 mL) and washed with saturated sodium bicarbonate solution (5 mL). The organic layer was washed with water (2 x 5 mL) then dried over sodium sulfate. Evaporation gave a yellow gum. Purification was performed by flash chromatography (4% methanol in dichloromethane) on silica gel (50 g). Pure fractions were combined and evaporated to give a colorless oil. The resulting product was dissolved in methanol (1 mL) and a solution of hydrochloric acid in ethyl ether (1.1M, 1.1 mL) was added. The reaction was stirred at RT for 10 min, then evaporated to dryness. The product was dried in a vacuum oven (55°C, 24 h) to give title compound (302 mg, 54%) as a white solid.

m.p. 161-165°C
MS (ESI, +ion): 647 (M+H)

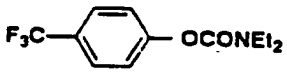
Anal. Calc. for $C_{38}H_{47}Cl_2F_3N_4O_2 \cdot 1.5\ H_2O$:
C, 61.12; H, 6.75; N, 7.50; Cl, 9.50; F, 7.63
Found: C, 60.97; H, 6.77; N, 7.40; Cl, 9.18; F, 7.34

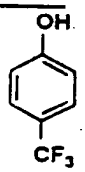
Example 4*

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4-(trifluoromethyl)[1,1-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride



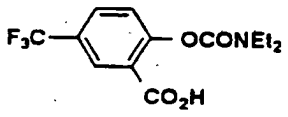
A.





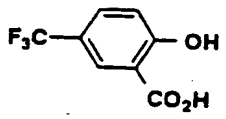
To a stirred solution of (3.08 g, 19.0 mmol) in THF (20 mL) at room temperature under argon was added triethylamine (2.80 mL, 20.0 mmol), diethyl carbamyl chloride (2.50 mL, 19.5 mmol) and dimethylaminopyridine (100 mg). The reaction was heated to 50°C for 18 h. The reaction was cooled, diluted with ether, washed with 10% citric acid solution, brine and dried ($MgSO_4$). Purification by flash chromatography on silica gel (5x15 cm column, 55:45 hexane/dichloromethane) provided title compound as a colorless oil, 4.35 g, 89%.

B.



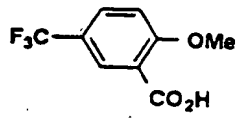
To a flame-dried three-necked flask fitted with a dropping funnel and thermometer under an argon atmosphere was added THF (100 mL) and N,N,N,N-tetramethylethylene diamine (TMEDA, 4.4 mL, 29.2 mmol). The resulting solution was cooled to -73°C and a solution of s-butyllithium in hexane (22.0 mL, 1.25 M, 27.5 mmol) was added dropwise over 1 min. After 30 min, a solution of Part A compound (5.90 g, 22.6 mmol) in THF (20 mL) was added over 20 min. After an additional hour, dry carbon dioxide gas was bubbled through the solution for 30 min. The cold bath was removed and the reaction was allowed to warm to 0°C. The turbid solution was immediately quenched with 10% citric acid solution, extracted twice with EtOAc, dried ($MgSO_4$) and evaporated to give title compound as a white solid, mp 124-126°C, 5.88 g, 85%.

C.



A slurry of Part B compound (2.28 g, 7.47 mmol) in 6 M hydrochloric acid (25 mL) under argon was heated to reflux for 1 h. The reaction was cooled, diluted with water, washed and filtered. The damp filter cake was dissolved in EtOAc, dried ($MgSO_4$) and evaporated to give title compound as a white solid, 1.52 g, 99%, mp 148-149°C.

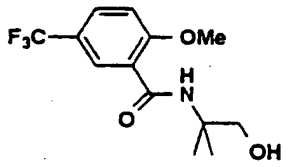
D.



To a stirred solution of Part C compound (1.50 g, 7.28 mmol) in DMF (20 mL) under argon at room temperature was added potassium carbonate (2.8 g, 20 mmol). The slurry was heated to 50°C and then dimethyl sulfate (1.9 mL, 20 mmol) was added. After 1 h, the reaction mixture was quenched with 10% citric acid solution (20 mL) and extracted twice with ether. The combined extracts were washed with water, dried ($MgSO_4$) and evaporated to give the methyl ester of title compound as a colorless oil, 1.71 g, 100%.

The oil was dissolved in THF (10 mL), 3 M sodium hydroxide solution (10 mL) was added and the mixture was heated to reflux under argon for 1 h. The solution was cooled, poured into cold 1 M hydrochloric acid and extracted twice with dichloromethane. The extracts were combined, dried ($MgSO_4$) and evaporated to give title compound as a white solid, 1.45 g, 91%, mp 105-107°C.

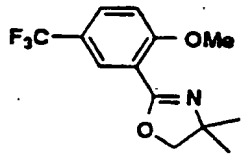
E.



To a stirred solution of Part D compound (1.40 g, 6.36 mmol) in dichloromethane (10 mL) protected by a Drierite-filled tube at room temperature was added oxalyl chloride (1.00 mL, 11.5 mmol) and DMF (50 mL). After 2 h, the solution was evaporated and redissolved in dichloromethane (20 mL). To this solution, under argon at room temperature, was added Et_3N (1.02 mL, 7.33 mmol) and then 2-amino-2-methyl-1-propanol (0.70 mL, 7.33 mmol). An exotherm results in an orange solution. After 13 h, the reaction

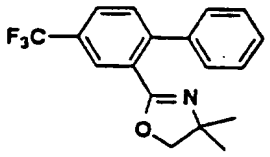
mixture was diluted with dichloromethane, washed twice with 10% citric acid solution, dried ($MgSO_4$) and evaporated to give title compound as a white foam, 2.08 g, >100% material balance.

F.



To a solution of Part E compound (2.08 g) in dichloromethane (20 mL) at room temperature and protected by a Drierite-filled tube was added thionyl chloride (1.9 mL, 23.6 mmol). The solution was stirred for 2 h, then diluted with dichloromethane and poured into a 1:1 mixture of ice and saturated sodium bicarbonate solution. The aqueous layer was adjusted to pH 8 with 1 M potassium hydroxide solution and extracted twice with dichloromethane. The organic extracts were combined, dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (5 x 10 cm column, 1:9 EtOAc/dichloromethane) provided title compound as a white solid, 1.56 g, 90% yield starting from Part D compound, mp 55-57°C.

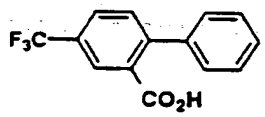
G.



To a stirred solution of Part F compound (1.17 g, 4.28 mmol) in THF (10 mL) at 0°C under argon was

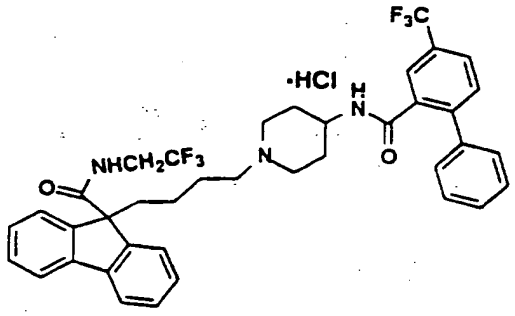
added a solution of phenylmagnesium bromide (1.7 mL, 3 M in ether, 5.1 mmol) over 5 min. After stirring an additional 10 min, the ice bath was removed and the reaction allowed to stir at room temperature. After 2 h, the reaction was quenched with saturated ammonium chloride solution and extracted twice with EtOAc. The extracts were combined, dried (Na_2SO_4) and evaporated to give a brown oil. Purification by flash chromatography on silica gel (5 x 15 cm column, 0.5 L hexane and then dichloromethane) provided title compound as a colorless oil, 1.36 g, 100%.

H.



A slurry of Part G compound (1.25 g, 3.91 mmol) in 6 M hydrochloric acid (25 mL) was heated to reflux for 13 h. The reaction mixture was cooled and extracted twice with dichlormethane. The extracts were combined, dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, EtOAc) provided title compound as a white solid, 395 mg, 38%, mp 120-122°C.

I.

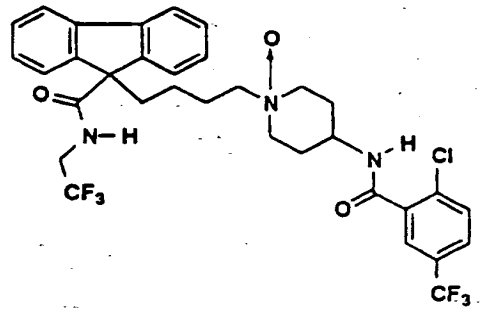


A solution of Part H compound (380 mg, 1.43 mmol) in thionyl chloride (3 mL) was stirred at room temperature, protected by a Drierite-filled tube. After 2 h, the reaction was evaporated and then re-evaporated from dichloromethane. The semi-solid residue was dissolved in dichloromethane (5 mL) and added dropwise to a solution, at 0°C under argon, of Example 11* Part C compound (816 mg, 1.57 mmol), Et_3N (0.7 mL, 5 mmol) and DMAP (50 mg, 0.4 mmol) in 10 mL of dichloromethane. After the addition was completed, the reaction was warmed to room temperature and stirred for 3 h. The reaction mixture was diluted with EtOAc, washed once with saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, 3:17 hexanes/EtOAc) provided title compound (as the free base) as a white foam, 640 mg, 65%. The foam was dissolved in dichloromethane (5 mL) and treated with 4 M hydrogen chloride in dioxane (0.3 mL). Evaporation provided title compound as the hydrogen chloride salt, 670 mg, mp 129-134°C.

Mass Spectrometry: (electrospray, + ions) m/z 694 (M+H).

Example 5*

9-[4-[4-[[2-Chloro-5-(trifluoromethyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide



To a solution of the Example 111* amine free base (8.50 g, 13.0 mmol) in methylene chloride (35 ml) was added a 35% of peracetic acid solution in acetic acid (3.7 ml, 15 mmol). An additional 3.7 mL of peracetic acid solution was added (15 mmol) after 1 h. The reaction mixture was stirred for 16 h at RT, diluted with toluene (200 mL) and the contents stripped. The residue was pumped to constant weight. The colorless remainder was diluted with $CHCl_3$/methanol (100 mL, 9:1) and concentrated to give an off-white solid foam which was recrystalized from a (10:1; 10 mL) dichloromethane/methanol solution. The yield of material was 2.3 g. The mother liquor was purified by flash column chromatography on silica gel with 7:93 methanol/dichloromethane to give 4.2 g of pure material. The solids were combined to give 6.5 g (75%) of title compound as a white solid.

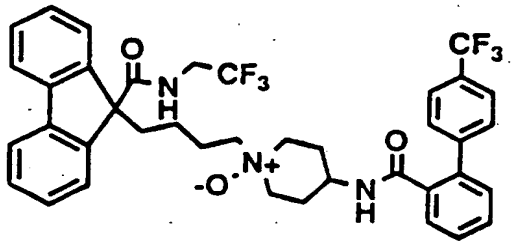
mp:131-136°C; material then resolidified:
mp: 198-200°C decomp.

MS (ES, + ions) m/z 668 (M+H). monochloro isotope pattern.

Anal Calcd. for $C_{33}H_{32}N_3O_3F_6Cl + H_2O$:
C, 57.77; H, 5.00; N, 5.78; Cl, 5.06
Found: C, 57.44; H, 5.11; N, 5.78; Cl, 5.06.

Example 6A*

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, N-oxide.

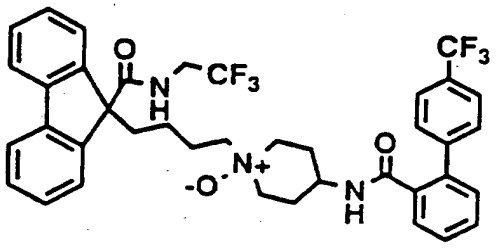


A CH_2Cl_2 (5 ml) solution of Example 10A* compound (200 mg, 0.274 mmol) was added to a 0°C solution of saturated $NaHCO_3$ (5 ml). After several minutes, a CH_2Cl_2 (2 ml) solution of *meta*-chloroperbenzoic acid (63 mg, 80%, 0.292 mmol) was added. A further amount of *meta*-chloroperbenzoic acid (23 mg, 80%, 0.107 mmol) was added in three portions over the next 1 h while the reaction was allowed to come to room temperature. The reaction mixture was partitioned between CH_2Cl_2 and saturated $NaHCO_3$ after 1.45 h. The aqueous layer was extracted twice with CH_2Cl_2, the organics dried over Na_2SO_4, and concentrated in vacuo to a colorless foam (200 mg). The residue was purified by flash column chromatography (silica gel, 50 ml), eluting with 5% MeOH:CH_2Cl_2, then 10% MeOH:CH_2Cl_2 with 1% NH_4OH, to give title compound (151 mg, 77.6% yield) as a colorless solid. mp 136-142°C [shrinks 115°C].

Rf = 0.38 (10% MeOH:CH_2Cl_2). MS: (electrospray, + ions) m/z 710^+(M+H).

Example 6B*

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[4'-(trifluoromethyl)[1,1-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, N-oxide.

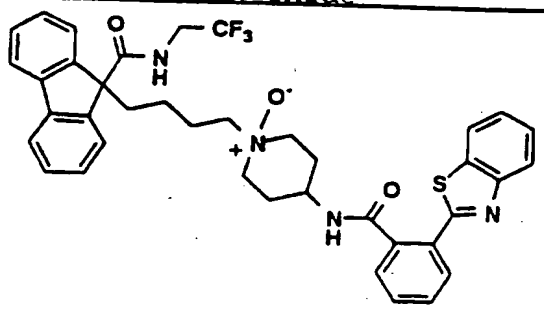


(Alternative Preparation)

To a CH_2Cl_2 (20 ml) solution of Example 10A* compound (5.3 g, 7.64 mmol) in an adiabatic water bath was added peracetic acid (1.7 ml, 32% in AcOH, 8.08 mmol). A further amount of peracetic acid (0.9 ml, 32% in AcOH, 4.28 mmol, 12.3 mmol total) was added in three portions over the next 1.5 h. The reaction mixture was partitioned between CH_2Cl_2 and 1N KOH, the aqueous layer extracted twice with CH_2Cl_2, the combined organics washed with H_2O, dried over Na_2SO_4, and concentrated in vacuo to a foam (4.95 g). The residue was crystalized from hot EtOH and H_2O to give a colorless solid containing still impure solid. The crude material (5.5 g, combined with an identical reaction starting with 0.93 mmol Example 10A* compound) could be purified by flash column chromatography (silica gel, 200 g), eluting with 10% MeOH:CH_2Cl_2 to give the title compound (3.5 g, 57% yield) as a colorless solid.

Example 7*

9-[4-[4-[[2-(2-Benzothiazolyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide

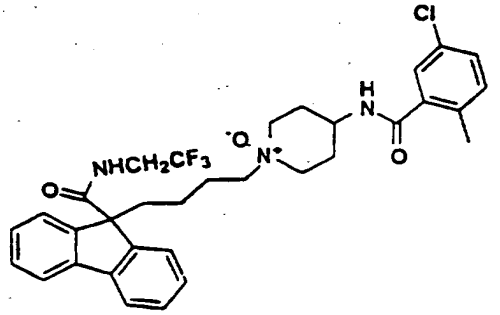


A solution Example 9* compound (free base, 14.589 g, 21.3 mmol) in CH_2Cl_2 (= 300 mL) at room temperature was treated with 4.40 mL 32% peracetic acid in dilute HOAc. After 2 hours, additional peracetic acid solution (1.2 mL) was added and stirring continued for 1 hour. The mixture was quenched with saturated $NaHCO_3$ and the CH_2Cl_2 layer was separated. The organic extract was washed with half-saturated NaCl, dried (Na_2SO_4), and filtered. The solution was diluted with EtOAc (= 200 mL) and let stand to give a white precipitate which was collected by filtration, washed with EtOAc and Et_2O, and dried in vacuo to give title compound (8.582 g, 55% corrected for solvent): mp 189-191°C.

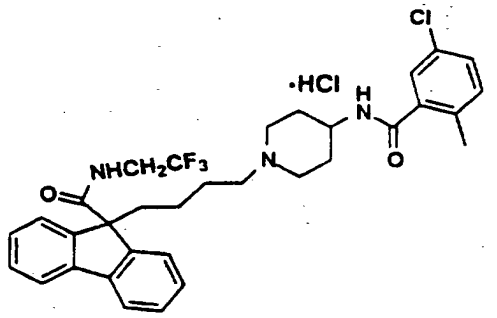
MS: ESI $(M+H)^+$ 699; $(M-H)^-$ 697.

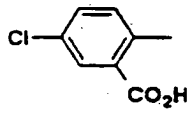
Example 8*

9-[4-[4-[(5-Chloro-2-methylbenzoyl)amino]-1-piper-idinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N'-oxide.



A.





To a stirred slurry of (2.05 g, 12.0 mmol), Example 11* Part C compound (6.22 g, 12.0 mmol), N-methylmorpholine (3.30 mL, 30.0 mmol) and HOBt•H_2O (1.80 g, 12.0 mmol) in dichlormethane (100 mL) at room temperature under argon was added EDAC (2.61 g, 13.7 mmol). Within 1 h, a clear yellow solution had formed. After 3 h, the reaction mixture was partitioned between EtOAc and saturated sodium bicarbonate solution. The organic extract was washed with brine, dried (Na_2SO_4) and evaporated. The resulting solid was recrystallized from EtOAc/hexanes to give the free base of the title compound, 6.56 g,

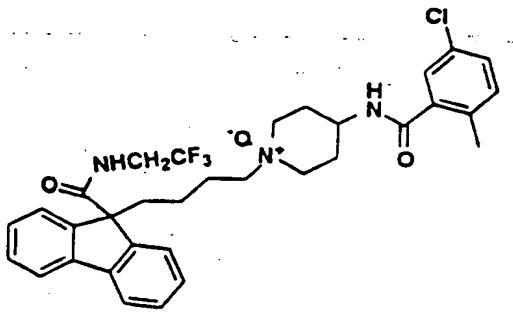
91%, mp 201-202°C. The free base was dissolved in dichloromethane (25 mL) and treated with 4 M hydrogen chloride in dioxane (3 mL). Evaporation provided title compound as the hydrogen chloride salt, an amorphous solid, 7.15 g, 100%

MICROAnal. Calcd for $C_{33}H_{35}ClF_3N_3O_2$ + HCl + 0.4 H_2O + 0.22 dioxane:

C, 61.55; H, 5.88; N, 6.36; Cl, 10.72

Found: C, 61.56; H, 5.86; N, 6.28; Cl, 10.95

B.



To a rapidly stirring slurry of Part A compound (635 mg, 1.00 mmol) and sodium bicarbonate (100 mg, 1.2 mmol) in dichloromethane (20 mL) and saturated sodium bicarbonate solution (5 mL) at room temperature under argon, was added m-chloroperbenzoic acid (mCPBA, 220 mg, 80% purity, 1.05 mol) portionwise over the course of 20 min. After 1 h, the reaction was diluted with dichloromethane and washed twice with saturated sodium bicarbonate solution. The organic layer was dried ($MgSO_4$) and evaporated. Purification by flash chromatography on silica gel (5 x 15 cm column, 3:17 methanol/EtOAc) followed by redissolving the evaporated residue in dichloromethane and filtration through a 2 mM nylon

filter provided title compound as a white solid, 450 mg, 73%, mp 124-127°C.

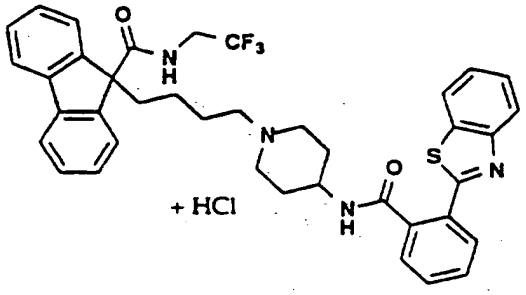
MICROAnal. Calcd for $C_{33}H_{35}ClF_3N_3O_3$ 1.5 H_2O + 0.6 EtOAc:

C, 61.27; H, 6.22; N, 6.22; Cl, 5.11; F, 8.21
Found: C, 61.33; H, 6.38; N, 6.09; Cl, 5.19; F, 8.21

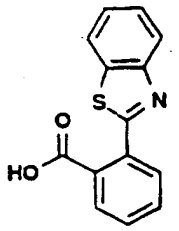
Mass Spectrometry: (electrospray, + ions)
m/z 614 (M+H)

Example 9*

9-[4-[4-[[2-(2-Benzothiazolyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.



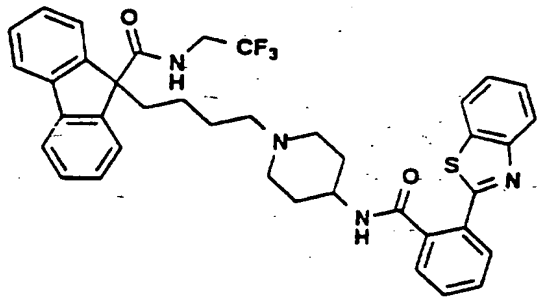
A.



A slurry of phthalic anhydride (7.1 g, 47.9 mmol) and 2-aminothiophenol (7.0 mL, 8.2 g, 65.4 mmol) in glacial acetic acid (50 mL) was heated at reflux for 3 hours. The cooled reaction mixture was poured into ≈ 400 mL ice water to give a gummy precipitate. The mixture was extracted with EtOAc

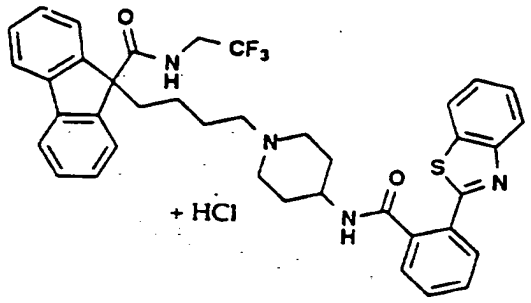
and the EtOAc extract was washed with 1 N HCl and H_2O. The organic layer was extracted three times with saturated $NaHCO_3$ and the pooled bicarbonate extracts were acidified with 6 N HCl to give a precipitate which was collected by filtration, washed with H_2O, and dried in vacuo to give title compound (11.27 g, 92%) as a white solid: mp 188-189°C.

B.



A slurry of Part A acid (2.048 g, 8.0 mmol) and Example 11* Part C diamine (3.960 g, 7.64 mmol) in CH_2Cl_2 (80 mL) was treated with N-methyl morpholine (2.1 mL, 1.93 g, 19.1 mmol) and DMF (6 mL). The slurry was then treated successively with HOBT hydrate (1.12 g, 8.3 mmol) and EDAC (1.630 g, 8.5 mmol). The mixture became homogeneous within 3 hours. After 4 hours, the solution was partitioned between EtOAc/Et_2O and saturated $NaHCO_3$. The organic layer was separated, washed twice with H_2O and brine, then dried (Na_2SO_4), filtered, and stripped. Flash chromatography (Merck SiO_2, 8/92-MeOH/CH_2Cl_2) gave title compound (5.369 g, 103% of theory, 96% corrected for solvent) as a white foam.

C.

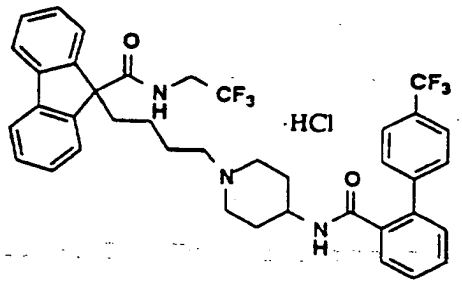


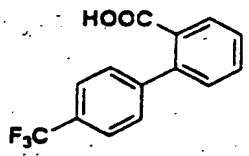
Part B compound (the free base, 5.254 g, 7.16 mmol corrected for solvent) was dissolved in ≈ 25 mL of 1,4-dioxane and treated with 2.2 mL of 4 N HCl in 1,4-dioxane at room temperature. The resulting homogeneous mixture was added via canula to ≈ 350 mL of Et_2O with rapid swirling. The precipitate was collected by filtration, washed with Et_2O, and dried in vacuo at 45°C to give title compound (5.113 g, 95% corrected for solvent) as a white solid.

MS (ESI): $(M+H)^+$ 683; $(M-H)^-$ 681.

Example 10A*

9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.





To a solution of the acid (3.2g, 12 mmol) in methylene chloride (35 ml) was added oxalyl chloride (1.8ml, 21 mmol) followed by a few drops of DMF. The reaction bubbled vigorously and stirred under argon at room temp 2h. The solvent was evaporated in vacuo at less than 25°C, and the residue was dissolved in methylene chloride (50 ml). This solution was added dropwise to a solution of the Example 11* Part C diamine (5.0g, 9.6 mmol) and triethylamine (6.7ml, 48 mmol) in methylene chloride (50 ml) at -5°C. The reaction stirred in a melting ice bath 1h. The reaction mixture was diluted with $MeCl_2$ and washed once with water. The organic layer was dried (Na_2SO_4), and the solvent was removed in vacuo to give an off-white solid foam which was purified by flash column chromatography (SiO_2, 800g) eluted with 5% MeOH:0.5%NH_4OH: $MeCl_2$ to give a clear oil (5.23g, 91.5% pure). This oil was purified again by flash column chromatography (SiO_2, 500g) eluted with 3%MeOH: $MeCl_2$ to give a clear oil (4.11g, 61.4% yield). This oil (4.07g) was dissolved in MeOH (25ml) and 1.1 N ethereal HCl (8.0ml) was added. The solvent was removed in vacuo to give title compound as a white solid foam (4.17g).

mp 129-142°C

MS (ESI, + ions) m/z 694 (M+H)

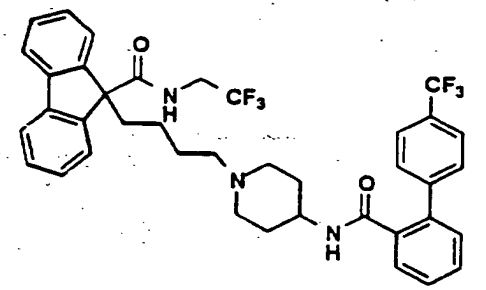
Anal. calc'd for $C_{39}H_{37}F_3N_2O_2 \cdot HCl + 1H_2O$:

C, 62.61; H, 5.39; N, 5.62

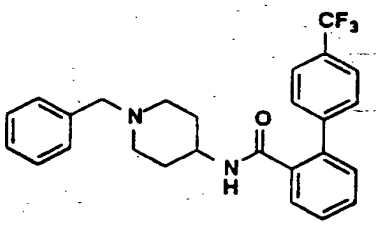
Found: C, 62.48; H, 5.19; N, 5.60

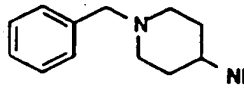
Example 10B*

9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.



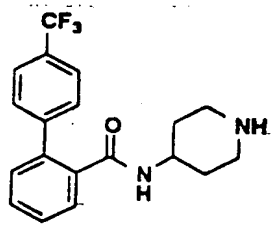
A.



To a slurry of 4'-(trifluoromethyl)-2-biphenyl carboxylic acid (50.0 g, 190 mmol) in methylene chloride (500 ml) was added the oxalyl chloride (28.7 ml, 330 mmol) followed by DMF (5 drops). The reaction bubbled vigorously and stirred at room temperature under argon 2 h. All solid had dissolved and evolution of gas had ceased. The solvent was removed in vacuo , and the residue was dissolved in methylene chloride (400 ml). This solution was added dropwise to a solution of compound  4-amino-1-benzylpiperidine (36.4 ml, 180 mmol) and triethylamine (65.4 ml, 470 mmol) in methylene chloride (300 ml) cooled in an ice/brine bath. After the addition was complete, a lot of solid had precipitated from solution. An additional 200 ml methylene chloride was added. The reaction stirred

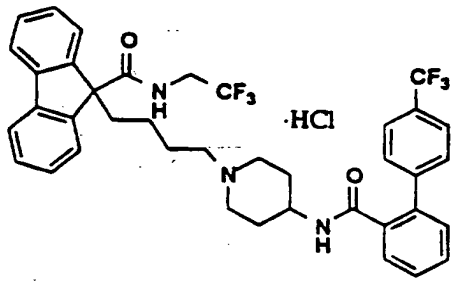
at room temperature under argon 18h. The reaction was diluted with methylene chloride (600 ml) and washed twice with saturated $NaHCO_3$, once with brine and once with 1N KOH. The organic layer was dried with Na_2SO_4, and the solvent removed in vacuo to give a white solid. This solid was recrystallized from hot EtOH (1 L) and washed with heptane to give title compound as a white solid (59.1 g, 75.6% yield). The mother liquor was concentrated to dryness and recrystallized from hot EtOH (300 ml) and washed with heptane to give a second crop of title compound as a white solid (12.7 g, 16.2% yield).

B.

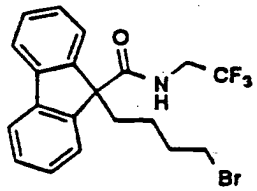


To a solution of Part A compound (59.0 g, 130 mmol) in methanol (300 ml) and ethanol (300 ml) was added the cyclohexene (150 ml, 1.5 mol) and 20% palladium hydroxide on carbon (11.8 g). The reaction was heated in an argon atmosphere to reflux (80°C) and stirred at that temperature 2.5 h. The hot mixture was filtered through Celite, washed with methanol and the solvent removed in vacuo to give title compound as a white solid (46.7 g, 99.6% yield).

C.



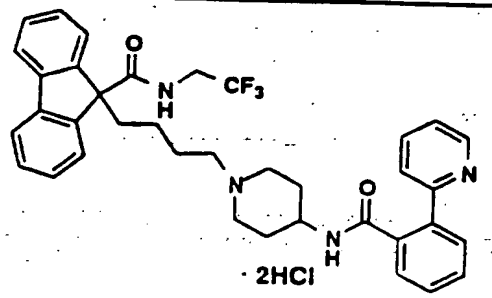
To a stirred solution of Part B compound (18.0g, 49 mmol) in DMF (100 ml) at room temperature under argon was added potassium carbonate (12.6g, 49 mmol) followed by



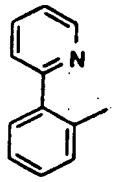
compound (prepared as described in Example 11* Part C(2)) (21.0g, 49 mmol). The reaction was heated to 50°C and stirred at that temp under argon 24h. After cooling, the reaction was filtered to remove potassium carbonate, and the filter cake was rinsed with ethyl acetate. The filtrate was partitioned between 20% heptane in ethyl acetate and water. The organic layer was washed five times with water and once with brine. The organic layer was dried (Na_2SO_4) and the solvent removed in vacuo to give a beige solid (30 g). This solid was recrystallized from 300 ml 25% EtOAc in heptane to give title compound as an off-white solid (27.0 g, 78.9% yield). mp 164-68°C.

Example 11*

9-[4-[4-[(2-Pyridinylbenzoyl)amino]-1-piperidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride

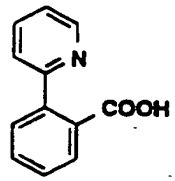


A.



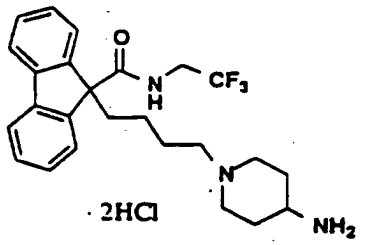
To a degassed solution of 2-bromopyridine (1.9 ml, 20 mmol) in ethylene glycol dimethyl ether (60 ml) under argon, tetrakis(triphenylphosphane) palladium^0 (700 mg, 0.6 mmol) was added. After stirring for 10 min., 2-methylphenyl boronic acid (2.9 g, 22 mmol) was added followed by sodium bicarbonate (5.04 g, 60 mmol in 60 ml water). The mixture was heated to reflux (~85°C) and stirred at that temp overnight. After cooling to room temp., the solvent was removed in vacuo, the residue was partitioned between water and ether, and the aqueous layer was extracted twice with ether. The combined organic layers were dried (Na_2SO_4), and the solvent was removed in vacuo to give a black oil. This oil was distilled under high vacuum at ~95°C to give title compound (2.75 g, 81.6% yield) as a clear oil.

B.

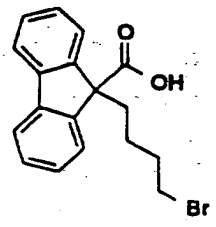


A solution of Part A compound (850 mg, 5.0 mmol) and potassium permanganate (1.9 g, 12.0 mmol) in water (25 ml) was heated to reflux (~100°C) and stirred at that temperature 1 h. The hot reaction mixture was filtered, and the filtrate was evaporated to dryness. The solid residue was dissolved in water (5 ml) and acidified with acetic acid to pH 4-5. The resulting precipitate was isolated by filtration and rinsed with water to give a white solid (800 mg) which was recrystallized from hot ethanol (12 ml) to give title compound as a white solid (453 mg, 45.3% yield).

C.

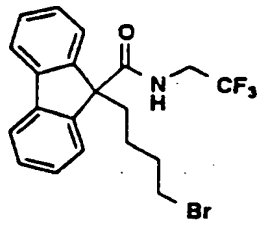


C(1).



To a solution of 9-fluorenecarboxylic acid (50 g, 240 mmol) in THF (1200 mL) at 0°C was added dropwise a solution of n-butyllithium (2.5M, 211 mL, 530 mmol) in THF. The yellow reaction was stirred at 0°C for 1 h, then 1,4-dibromobutane (31.3 mL, 260 mmol) was added dropwise over 30 min. The reaction was stirred at 0°C for 30 min, then the reaction was warmed to RT for 30 h. The reaction was extracted with water (3 x 750 mL). The combined aqueous layers were extracted with ethyl ether (800 mL). The aqueous layer was made acidic with HCl solution (1N, 500 mL), then extracted with dichloromethane (3 x 750 mL). The combined organic layers were dried over $MgSO_4$. Evaporation gave title compound (71 g, 85%) as a white solid.

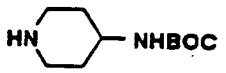
C(2).



To a solution of Part C(1) acid (60 g, 173 mmol) and DMF (100 µL) in CH_2Cl_2 (600 mL) under argon at 0°C was added oxalyl chloride (104 mL, 2.0M in CH_2Cl_2, 208 mmol) dropwise. The reaction was stirred at 0°C for 10 min, then warmed to RT and stirred for 1.5 h. The reaction was concentrated in vacuo to give the crude acid chloride as a yellow oil. To a suspension of 2,2,2-trifluoroethylamine hydrochloride (25.9 g, 191 mmol) in CH_2Cl_2 (500 mL) at 0°C under argon was added triethylamine (73 mL, 521 mmol) followed by dropwise addition of a solution of the

crude acid chloride in CH_2Cl_2 (15 mL). The reaction was stirred at 0°C for 1 h, diluted with CH_2Cl_2 (500 mL), and washed with water (2 x 300 mL), 1N HCl (2 x 300 mL), saturated $NaHCO_3$ (2 x 300 mL), and brine (2 x 300 mL), then dried over $MgSO_4$. Evaporation gave 80 g of a oil which was purified by flash chromatography on silica gel (2.5 kg). The crude product was loaded in a mixture of CH_2Cl_2 and hexane, and eluted with a step gradient of 10% EtOAc/hexane (4L) to 15% EtOAc/hexane (2L) to 20% EtOAc/hexane (4L). Pure fractions were combined and evaporated to give title compound (52.5 g, 71%) as a white solid (mp 88-92°C).

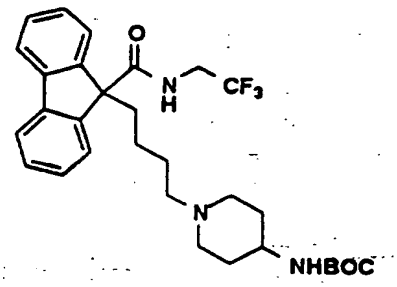
C(3).



To a solution of 4-aminobenzylpiperidine (20 g, 105 mmol) in dichloromethane (200 mL) at 0°C was added dropwise (about 30 min) a solution of di-tert-butyldicarbonate (25.2 g, 115 mmol) in dichloromethane (50 mL). The reaction was stirred at RT for 2 h, then evaporated to give an off-white solid. The product was triturated with ethyl ether (2 X 20 mL) to give a white solid (26.5 g, 90%). The product was dissolved in ethanol (200 mL). To the resulting solution at RT was added glacial acetic acid (10 mL, 177 mmol) and 10% palladium on activated carbon (2.6 g). Hydrogenation on a Parr apparatus (Initial pressure 40 psi) was maintained for 19 h. The reaction was filtered through Celite and the filtrate was concentrated to dryness. The residue was dissolved in chloroform (500 mL) and washed with 1N KOH saturated with sodium chloride (3 x 100 mL).

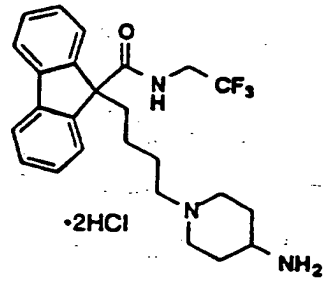
The aqueous layers were combined and extracted with chloroform (3 x 80 mL). Combined organics were dried over sodium sulfate and evaporated to give title compound (16 g, 90%) as a white solid (m.p. 157-159°C).

C(4).



A mixture of Part C(2) compound (29.5 g, 69.2 mmol), Part C(3) compound (14.5 g, 72.7 mmol), and anhydrous potassium carbonate (11.5 g, 83.0 mmol) in DMF (100 mL) was stirred at 50°C for 48 h, concentrated to dryness, and taken up in CH_2Cl_2 (500 mL). The solution was washed with saturated $NaHCO_3$ (3 x 80 mL) and brine (2 x 80 mL), then dried over $MgSO_4$. Evaporation gave a yellow oil which was purified by flash chromatography on silica gel (600 g), loaded in CH_2Cl_2, and eluted with a step gradient of 2% MeOH/CH_2Cl_2 (3L) to 3% MeOH/CH_2Cl_2 (4L). Pure fractions were combined and evaporated to give title compound (30 g, 86%) as a white foamy gum.

C(5).



To a solution of Part C(4) compound (30.5 g, 60.4 mmol) in dioxane (120 mL) was added 4N HCl in dioxane (121 mL, 483 mmol). The reaction was stirred at RT for 4 h, then concentrated in vacuo to provide title compound (30 g) as a white foamy solid, containing a residual amount of dioxane.

D. 9-[4-[4-[(2-Pyridinylbenzoyl)amino]-1-piperidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride

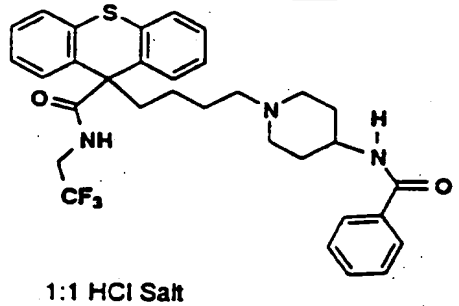
To a solution of the Part B acid (145 mg, 0.7 mmol) in methylene chloride (2 ml) was added oxalyl chloride (110 µl, 1.3 mmol) followed by a few drops of DMF. The reaction bubbled vigorously, turned yellow, and stirred under argon at room temp 2 h. The solvent was evaporated in vacuo at less than 25°C, and the residue was dissolved in methylene chloride (5 ml). This solution was added dropwise to a solution of the Part C diamine (300 mg, 0.6 mmol) and triethylamine (400 µl, 2.9 mmol) in methylene chloride (5 ml) at -5°C. The reaction stirred in a melting ice bath overnight. The reaction mixture was diluted with $MeCl_2$ and washed once with water. The organic layer was extracted twice with 1N HCl. The combined acid extractions were made basic with 1N NaOH and extracted twice with EtOAc. The combined

EtOAc layers were dried (Na_2SO_4), and the solvent was removed in vacuo to give a brown oil which was purified by flash column chromatography (SiO_2, 90g) eluted with 5% MeOH: 0.5% NH_4OH:$MeCl_2$ to give a clear oil (170 mg, 46.8% yield). 160 mg of this oil was dissolved in MeOH (2 ml) and 1.1 N ethereal HCl (800 µl) was added. The solvent was removed in vacuo to give title compound as a light yellow solid (173 mg).

mp 146-50 °C (dec.)
MS (ESI, + ions) m/z 627 (M+H)
Anal. calc'd for $C_{37}H_{37}F_3N_4O_2 \cdot 2HCl + 2H_2O$:
C, 60.41; H, 5.89; N, 7.62
Found: C, 60.38; H, 5.86; N, 7.50

The following additional compounds were prepared employing procedures as set out hereinbefore.

Example 11a*



1:1 HCl Salt

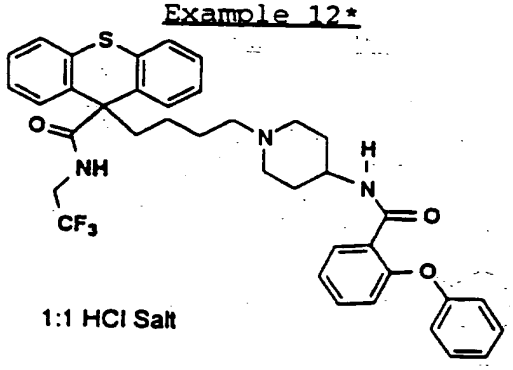
9-[4-[4-(Benzoylamino)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide, monohydrochloride.

M.P. 145-150°C
MS (ES, + ions) m/z 582 (M+H)

Elemental Anal. Calc'd for $C_{32}H_{34}N_3O_2F_3S$ + 1.0 HCl + 0.75 H_2O:

C, 60.94; H, 5.67; N, 6.66; F, 9.04
Found: C, 60.97; H, 6.00; N, 6.26; F, 9.15.

Example 12*



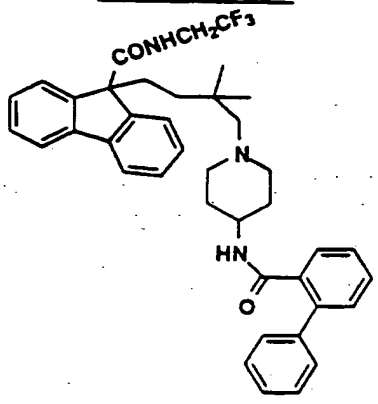
1:1 HCl Salt

9-[4-[4-[(2-Phenoxybenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide, monohydrochloride.

M.P. 204-208°C
MS (ES, + ions) m/z 578 (M+H)
Elemental Anal. Calc'd for $C_{38}H_{38}O_3SF_3N_3$ + 1 HCl+0.5 H_2O:

C, 63.46; H, 5.61; N, 5.84; S, 4.46
Found: C, 63.45; H, 5.51; N, 5.72; S, 4.15.

Example 13*

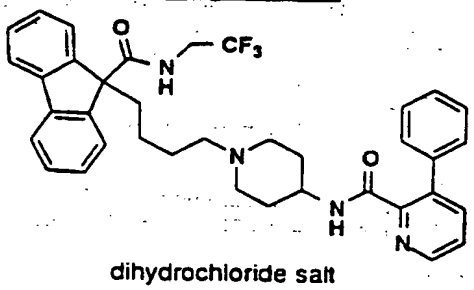


9-[4-[4-[([1,1-Biphenyl]-4-ylcarbonyl)amino]-1-piperidinyl]-3,3-dimethylbutyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 95-101°C

MS (electrospray, - ions) m/z 654 (M+H)

Example 14*

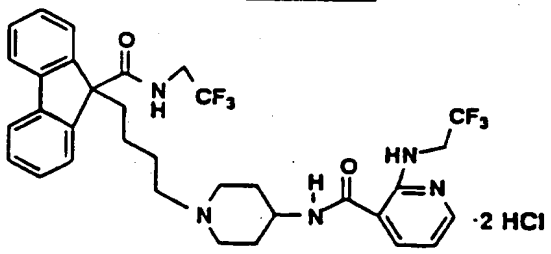


dihydrochloride salt

9-[4-[4-[[(3-Phenyl-2-pyridinyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride salt.

MS (ESI, + ions) m/z 627 $(M+H)^+$; (ESI, - ions) m/z 625 $(M-H)^-$

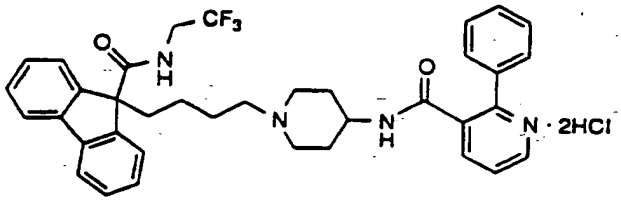
Example 15*



N-[1-[4-[9-[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluorene-9-yl]but-1-yl]piperidin-1-yl]-2-[N-(2,2,2-trifluoroethyl)amino]pyridine-3-carboxamide, hydrochloride.

MS (ESI, + ions) m/z 648 (M+H); (ESI, - ions) m/z 646 (M-H)

Example 16*

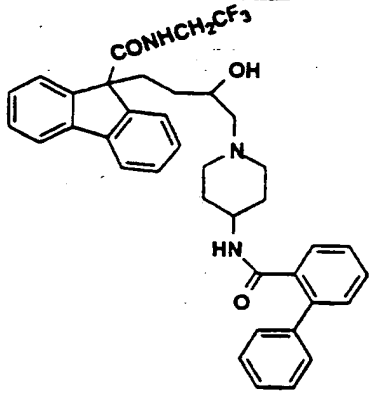


contains 0.1 mole of ethyl ether

N-[1-[4-[9-[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]but-1-yl]piperidin-4-yl]-2-phenyl-pyridine-3-carboxamide, hydrochloride.

MS (ESI-NH_3, + ions) 627 (M+H)

Example 17*

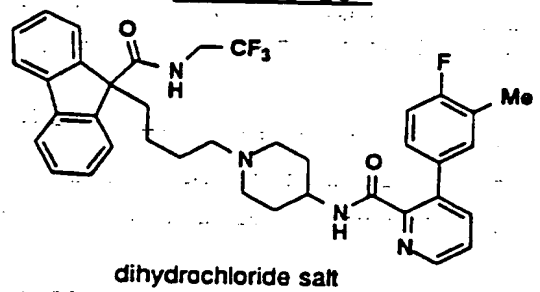


9-[4-[4-[([1,1-Biphenyl]-4-ylcarbonyl)amino]-1-piperidinyl]-3-hydroxybutyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 163-165°C

MS (electrospray, + ions) m/z 642 (M+H)

Example 18*



dihydrochloride salt

9-[4-[4-[[[3-(4-Fluoro-3-methylphenyl)-2-pyridinyl]-carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

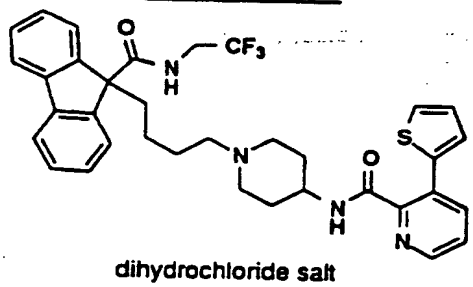
MS (ESI, + ions) m/z 659 $(M+H)^+$; (ESI, - ions) m/z 657 $(M-H)^-$

Elemental Anal. Calc'd for $C_{38}H_{38}F_4N_4O_2$+2 HCl + 1.5 H_2O + 0.2 Et_2O + 0.2 dioxane

C, 60.12; H, 5.94; N, 7.08; F, 9.61; Cl, 8.96

Found: C, 60.17; H, 5.89; N, 7.24; F, 10.48; Cl, 8.91

Example 19*

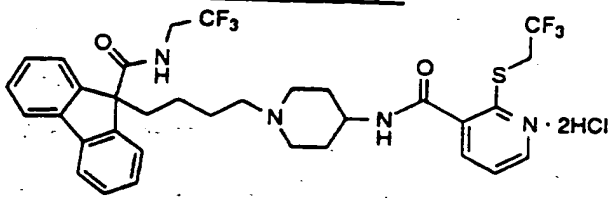


dihydrochloride salt

9-[4-[4-[[[3-(2-Thienyl)-2-pyridinyl]carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

MS (ESI, + ions) m/z 633 $(M+H)^+$; (ESI, - ions) m/z 631 $(M-H)^-$

Example 20*

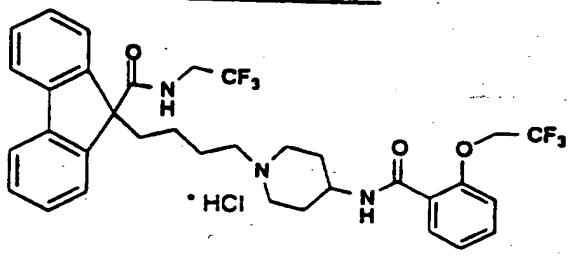


contains 0.15 mole of ethyl ether

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[2-[(2,2,2-trifluoroethyl)thio]-3-pyridinyl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, dihydrochloride.

MS (ESI-NH_3, + ions) 665 (M+H); 663 [M-H]

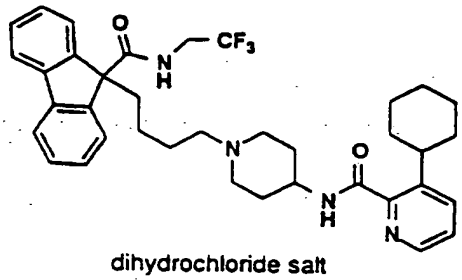
Example 21*



9-[4-[4-[[2-(2,2,2-Trifluoroethoxy)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

MS (electrospray, + ions) m/z 648 (M+H)

Example 22*



dihydrochloride salt

9-[4-[4-[[(3-Cyclohexyl-2-pyridinyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

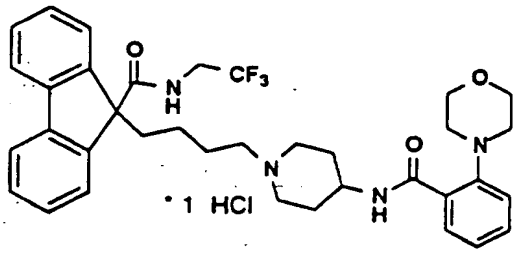
MS (ESI, + ions) m/z 633 $(M+H)^+$; (ESI, - ions) m/z 631 $(M-H)^-$

Elemental Anal. Calc'd for $C_{37}H_{42}F_3N_4O_2$+2 HCl + 1.5 H_2O + 0.25 Et_2O:

C, 60.69; H, 6.60; N, 7.45; F, 7.58; Cl, 9.43

Found: C, 60.89; H, 6.98; N, 7.51; F, 7.25; Cl, 9.83

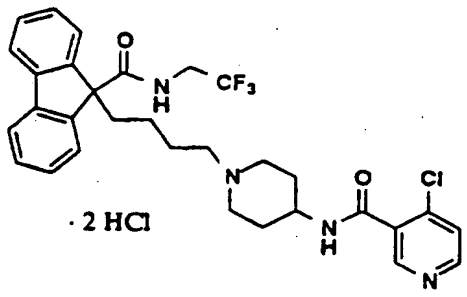
Example 23*



9-[4-[4-[[2-(4-Morpholinyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

MS (electrospray, + ions) m/z 635 (M+H)

Example 24*

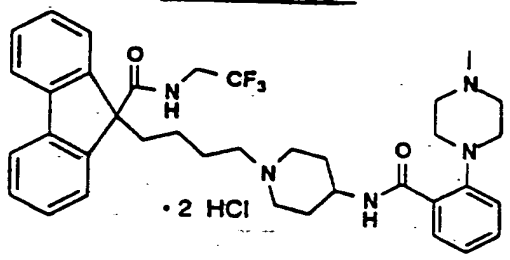


9-[4-[4-[(4-Chloro-3-pyridinyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

M.P. 165-73°C

MS (ESI, + ions) m/z 585 (M+H)

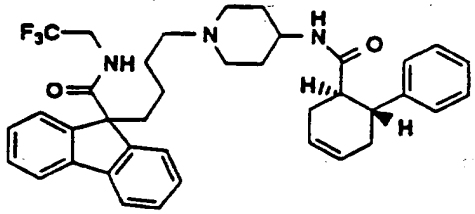
Example 25*



9-[4-[4-[[2-(4-Methyl-1-piperazinyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

MS (electrospray, + ions) m/z 648 (M+H)

Example 26*

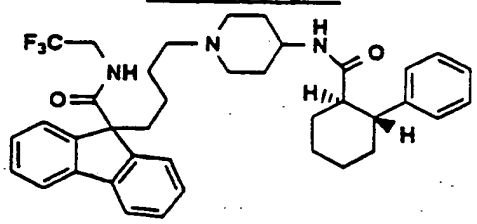


trans-9-[4-[4-[[(1-Phenyl-3-cyclohexen-1-yl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 160-163°C

MS (electrospray, + ions) m/z 630 (M+H)

Example 27*

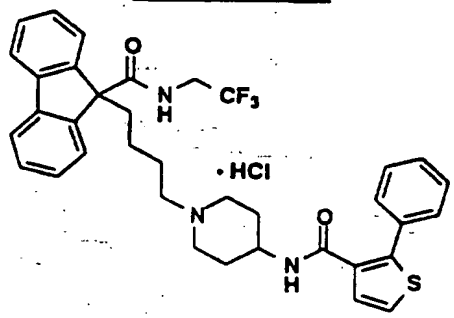


trans-9-[4-[4-[[(2-Phenylcyclohexyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 156-159°C

MS (electrospray, + ions) m/z 632 (M+H)

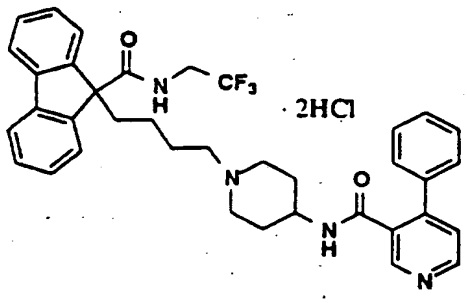
Example 28*



9-[4-[4-[[(2-Phenyl-3-thienyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

MS (ES, + ions) m/z 632 (M+H)

Example 29*



9-[4-[4-[(4-Phenyl-3-pyridinyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

M.P. 144-50°C

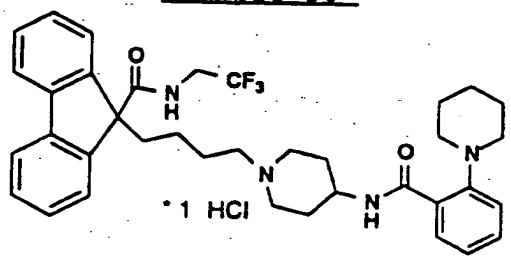
MS (ESI, + ions) m/z 627 (M+H)

Elemental Anal. Calc'd for $C_{37}H_{37}F_3N_4O_2$ + 2 HCl + 1.2 H_2O:

C, 61.62; H, 5.79; N, 7.77

Found: C, 61.64; H, 5.80; N, 7.32

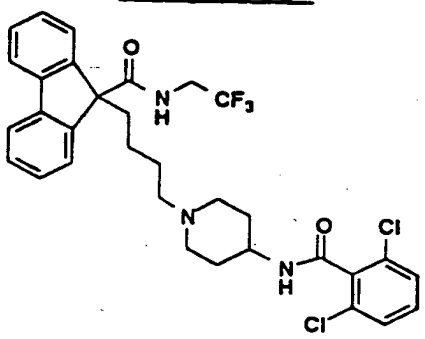
Example 30*



9-[4-[4-[[2-(1-Piperidinyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

MS (electrospray, + ions) m/z 633 (M+H)

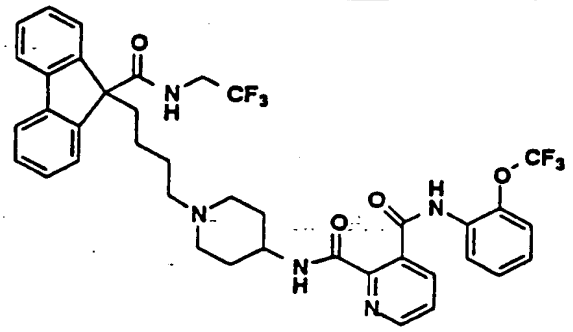
Example 31*



• TFA

MS (ESI, + ions) m/z 618 (M+H)

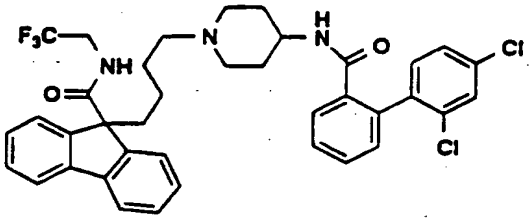
Example 32*



• TFA

MS (ESI, + ions) m/z 754 (M+H)

Example 33*

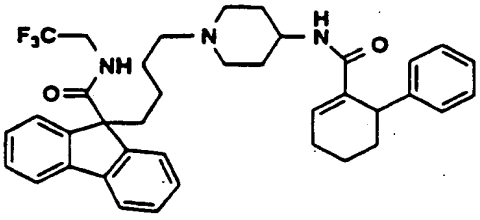


9-[4-[4-[[2-(2,4-Dichlorophenyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 123-128°C

MS (electrospray, - ions) m/z 694 (M+H)

Example 34*

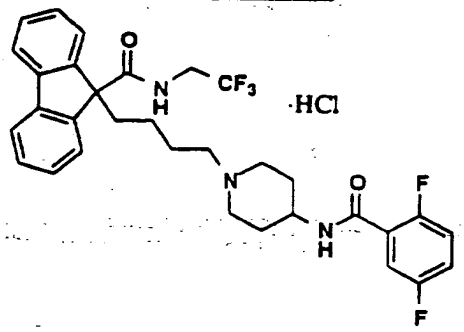


9-[4-[4-[[(6-Phenyl-1-cyclohexen-1-yl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 110-114°C

MS (electrospray, - ions) m/z 630 (M+H)

Example 35*



9-[4-[4-[(2,5-Difluorobenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 80-84°C

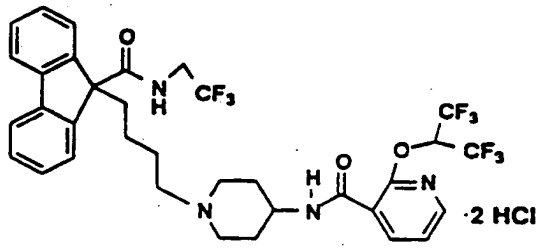
MS (ESI, + ions) m/z 586 (M+H)

Elemental Anal. Calc'd for $C_{32}H_{32}F_5N_3O_2$ + 1 HCl + 1.2 H_2O:

C, 59.71; H, 5.54; N, 6.53

Found: C, 59.68; H, 5.53; N, 6.44

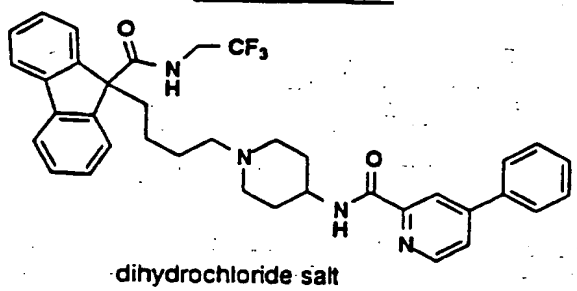
Example 36*



9-[4-[4-[[[2-[2,2,2-Trifluoro-1-(2,2,2-trifluoromethyl)ethoxy]-3-pyridinyl]carbonyl]-amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

MS (ESI, + ions) 717 (M+H); (-ions) 715 (M-H)

Example 37*



dihydrochloride salt

9-[4-[4-[[(4-Phenyl-2-pyridinyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

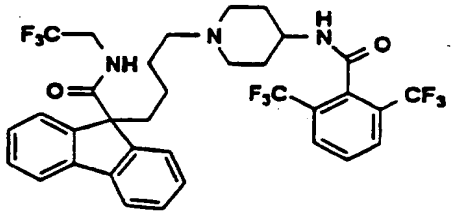
MS (ESI, + ions) m/z 627 $(M+H)^+$; (ESI, - ions) m/z 625 $(M-H)^-$

Elemental Anal. Calc'd for $C_{37}H_{37}F_3N_4O_2$ + 2 HCl + 0.44 Et_2O + 3.0 H_2O:

C, 59.21; H, 6.33; N, 7.13; F, 7.25; Cl, 9.02

Found: C, 59.59; H, 6.01; N, 6.97; F, 7.10; Cl, 9.17

Example 38*

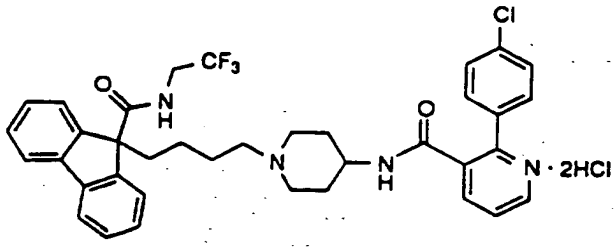


9-[4-[4-[[2,6-Bis(trifluoromethyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 145-150°C

MS (electrospray, - ions) m/z 686 (M+H)

Example 39*

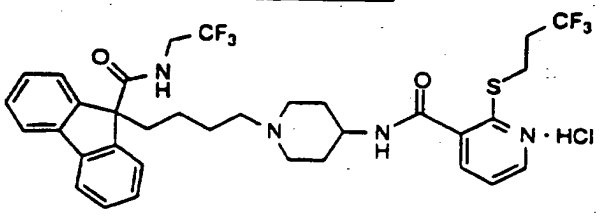


contains 0.05 mole of ethyl ether

9-[4-[4-[[[2-(4-Chlorophenyl)-3-pyridinyl]carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

MS (ESI-NH_3, + ions) (M+H) 661

Example 40*

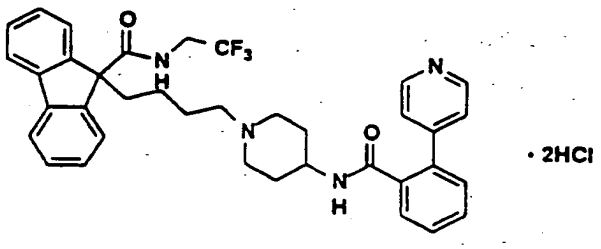


contains 0.12 mole of ethyl ether

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[2-[(3,3,3-trifluoropropyl)thio]-3-pyridinyl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

MS (ESI-NH_3, + ions) (M+H) 679

Example 41*

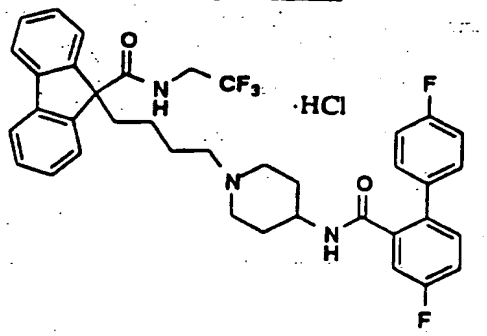


9-[4-[4-[[2-(4-Pyridinyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

M.P. 140-150°C (shrinking commencing at 115°C)
MS (electrospray, - ions) m/z 627 $(M+H)^+$
Elemental Anal. Calc'd for $C_{37}H_{37}F_3N_4O_2 \cdot 2\ HCl \cdot 2.14\ H_2O$:

C, 60.21; H, 5.91; N, 7.59; Cl, 9.60; F, 7.72
Found: C, 60.21; H, 6.08; N, 8.01; Cl, 9.23; F, 7.37

Example 42*

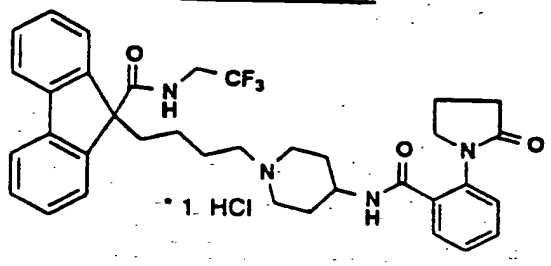


9-[4-[4-[[(4,4'-Difluoro[1,1'-biphenyl]-2-yl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 131-34°C
MS (ESI, + ions) m/z 662 (M+H)
Elemental Anal. Calc'd for $C_{38}H_{36}F_5N_3O_2 + HCl + 1.7\ H_2O$:

C, 62.63; H, 5.59; N, 5.77
Found: C, 62.59; H, 5.29; N, 5.82

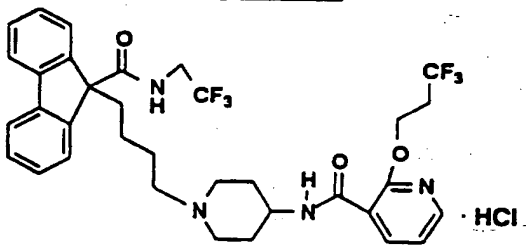
Example 43*



9-[4-[4-[[2-(2-Oxo-1-pyrrolidinyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

MS (electrospray, + ions) m/z 633 (M+H)

Example 44*



Contains: $1.25H_2O \cdot 0.12H_5C_2OC_2H_5$

N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[2-(3,3,3-trifluoropropoxy)-3-pyridinyl]carbonyl]-amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

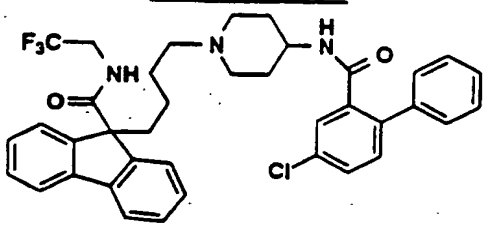
MS (ESI, + ion) m/z 663 (M+H); (-ion) 661 (M-H)

Elemental Anal. Calc'd for $C_{34}H_{36}N_4O_3F_6 \cdot HCl \cdot 1.25 H_2O \cdot 0.12 H_5C_2OC_2H_5$

C, 56.69; H, 5.62; N, 7.67; Cl, 4.85; F, 15.60

Found: C, 56.98; H, 5.52; N, 7.63; Cl, 4.74; F, 15.31

Example 45*

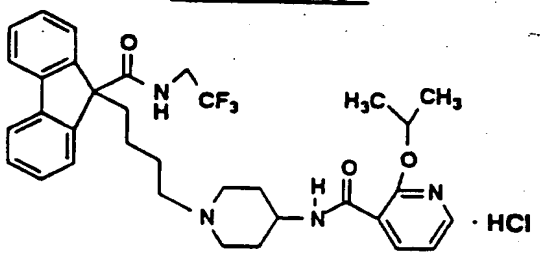


9-[4-[4-[[(4-Chloro[1,1-biphenyl]-2-yl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 123-128°C

MS (electrospray, - ions) m/z 661 (M+H)

Example 46*



Contains: $0.8H_2O$

9-[4-[4-[[[2-(1-Methylethoxy)-3-pyridinyl]carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

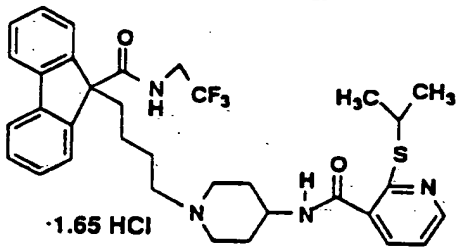
MS (ESI, + ion) m/z 609 (M+H); (-ion) 607 (M-H)

Elemental Anal. Calc'd for $C_{34}H_{39}N_4O_3F_3 \cdot HCl \cdot 0.8 H_2O$:

C, 61.91; H, 6.36; N, 8.49; Cl, 5.38; F, 8.64

Found: C, 61.63; H, 6.45; N, 8.31; Cl, 5.80; F, 8.50

Example 47*



Contains: $1.5H_2O$

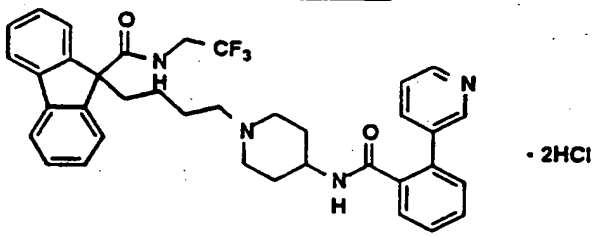
9-[4-[4-[[[2-[(1-Methylethyl)thio]-3-pyridinyl]carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

MS (ESI, + ion) m/z 625 (M+H); (-ion) 623 (M-H)
Elemental Anal. Calc'd for $C_{34}H_{39}N_4O_2SF_3 \cdot 1.65\ HCl \cdot 1.5\ H_2O$:

C, 57.36; H, 6.18; N, 7.87; Cl, 8.22; F, 8.01; S, 4.50

Found: C, 57.56; H, 6.37; N, 7.74; Cl, 8.12; F, 8.06 S. 4.47

Example 48*



contains 2.14 moles H_2O
Eff. Mol Wt. = 738.105

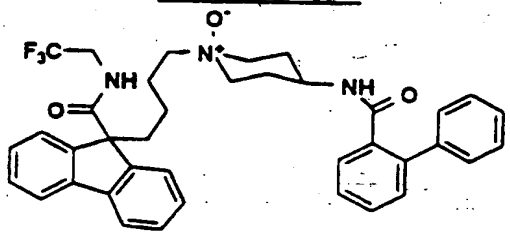
9-[4-[4-[[2-(3-Pyridinyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

M.P. 120-130°C (shrinking commencing at 110°C)
MS (electrospray, - ions) m/z $(M+H)^+$ = 627

Elemental Anal. Calc'd for $C_{37}H_{37}F_3N_4O_2 \cdot 2\ HCl \cdot 2.14\ H_2O$:

C, 60.21; H, 5.91; N, 7.59; Cl, 9.60; F, 7.72;
Found: C, 60.26; H, 6.26; N, 7.04; Cl, 9.09; F, 7.15

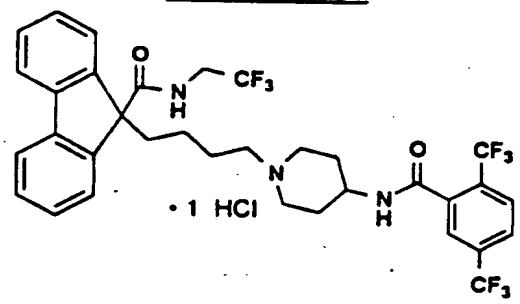
Example 49*



9-[4-[4-[([1,1-Biphenyl]-4-ylcarbonyl)amino]-1-piperidinyl]-3,3-difluorobutyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide.

M.P. 185-188°C
MS (electrospray) $(M+H)^+$ 642; $(M-H)^-$ 640

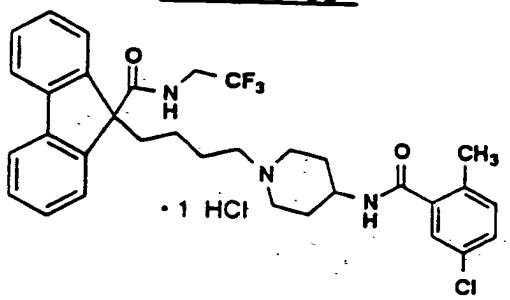
Example 50*



9-[4-[4-[[2,5-Bis(trifluoromethyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

MS (electrospray, + ions) m/z 686 (M+H)

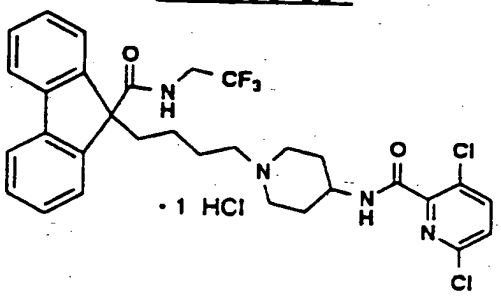
Example 51*



9-[4-[4-[(5-Chloro-2-methylbenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

MS (electrospray, + ions) m/z 598 (M+H)

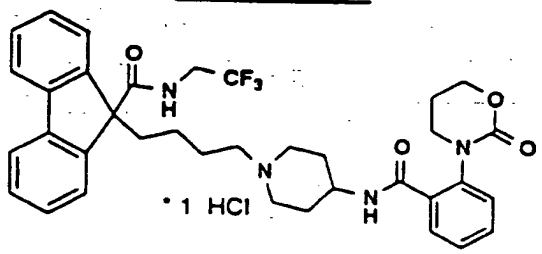
Example 52*



9-[4-[4-[[(3,6-Dichloro-2-pyridinyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

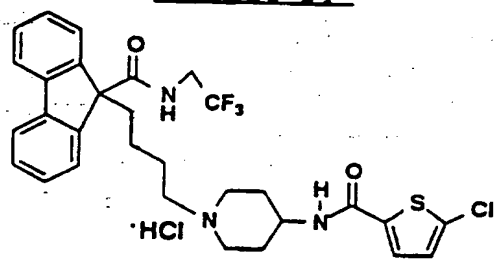
MS (electrospray, + ions) m/z 619 (M+H) [2 Cl isotope pattern]

Example 53*



9-[4-[4-[[2-(Tetrahydro-2-oxo-2H-1,3-oxazin-3-yl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

Example 54*



Contains: 0.6 H_2O·0.2 $H_5C_2OC_2H_5$

9-[4-[4-[[(5-Chloro-2-thienyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

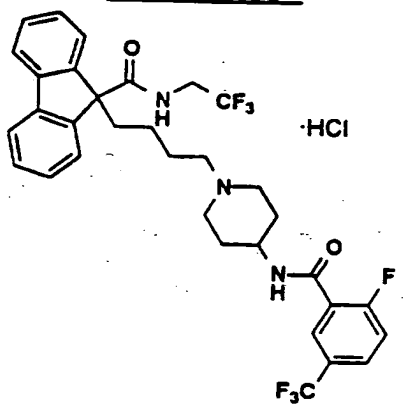
MS (ESI, + ion) m/z 590 (M+H) 1Cl Isotope Pattern

Elemental Anal. Calc'd for $C_{30}H_{31}N_3O_2ClSF_3 \cdot HCl \cdot 0.6 H_2O \cdot 0.2 H_5C_2OC_2H_5$:

C, 56.72; H, 5.44; N, 6.44; Cl, 10.87; F, 8.74 S, 4.92

Found: C, 56.43; H, 5.37; N, 6.38; Cl, 10.70; F, 8.73 S, 5.36

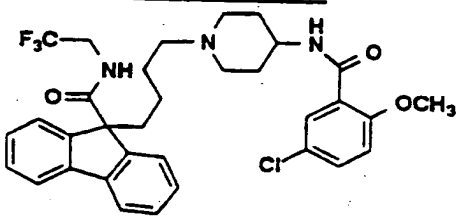
Example 55*



9-[4-[4-[[2-Fluoro-5-(trifluoromethyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

$(M+H)^+$ 636; $(M-H)^-$ 634

Example 56*

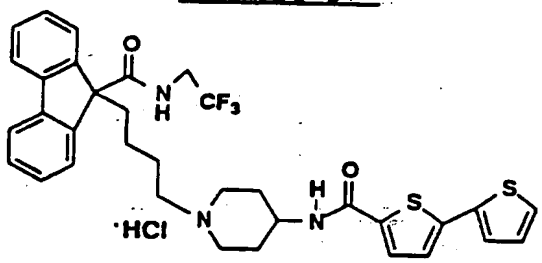


9-[4-[4-[(5-Chloro-2-methoxybenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 108-113°C

MS (electrospray, - ions) m/z 615 (M+H)

Example 57*



Contains: $H_2O \cdot 0.15\ H_5C_2OC_2H_5$

9-[4-[4-[[(2:2'-Bithiophen-5-yl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

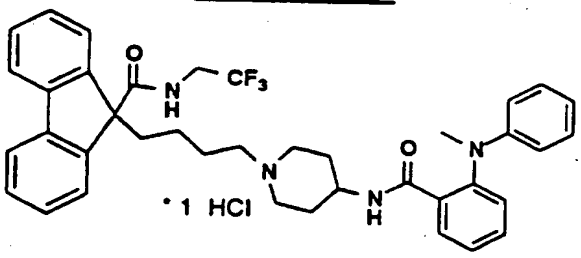
MS (ESI, + ion) m/z 638 (M+H)

Elemental Anal. Calc'd for $C_{34}H_{34}N_3O_2S_2F_3 \cdot HCl \cdot H_2O \cdot 0.15\ H_5C_2OC_2H_5$:

C, 59.08; H, 5.52; N, 5.97; Cl, 5.04; F, 8.10 S, 9.12

Found: C, 58.88; H, 5.41; N, 5.90; Cl, 4.97; F, 8.24 S, 9.22

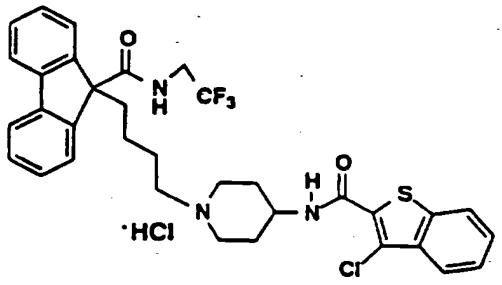
Example 58*



9-[4-[4-[[2-(Phenylmethylamino)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

ESI $(M+H)^+$ 655

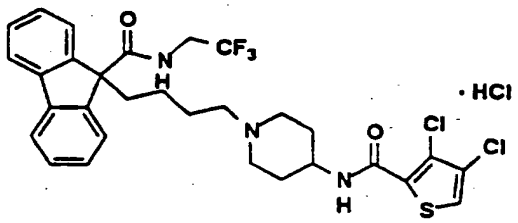
Example 59*



9-[4-[4-[[(3-Chlorobenzo[b]thiophen-2-yl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

MS (ESI, + ions) m/z 640 (M+H) 1 Cl Isotope pattern

Example 60*

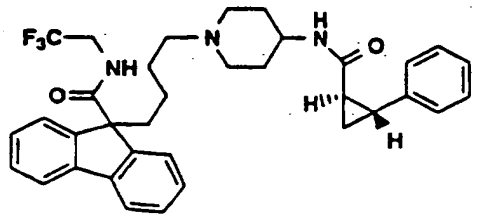


9-[4-[4-[[(3,4-Dichloro-2-thienyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 110-120°C (shrinking commencing at 95°C

MS (electrospray, - ions) m/z (M+H) 624; 2 Cl isotope pattern

Example 61*



trans-9-[4-[4-[[(2-Phenylcyclopropyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 118-126°C

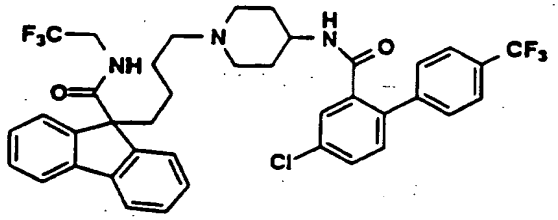
MS (electrospray, - ions) m/z 590 (M+H)

Elemental Anal. Calc'd for $C_{35}H_{38}F_3N_3O_2$ + HCl + 0.82 H_2O + 0.36 dioxane

C, 65.07; H, 6.52; N, 6.25; Cl, 5.27; F, 8.47

Found: C, 65.07; H, 6.50; N, 6.12; Cl, 5.36; F, 8.25

Example 62*



9-[4-[4-[[[4-Chloro-4'-(trifluoromethyl)[1,1-biphenyl]-2-yl]-carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, monohydrochloride

M.P. 123-128°C

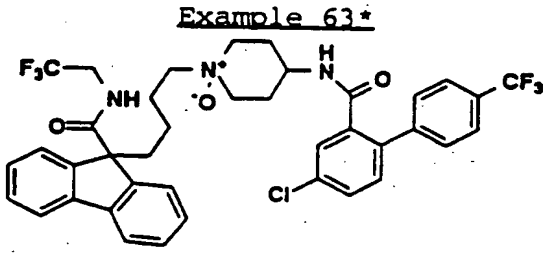
MS (electrospray, - ions) m/z 728 (M+H)

Elemental Anal. Calc'd for $C_{39}H_{36}ClF_6N_3O_2$+HCl+0.5 H_2O:

C, 60.55; H, 4.95; N, 5.43; Cl, 9.17

Found: C, 60.54; H, 4.84; N, 5.22; Cl, 8.91

Example 63*



9-[4-[4-[[[4-Chloro-4'-(trifluoromethyl)[1,1'-biphenyl]-2-yl]carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide.

M.P. 142-144°C

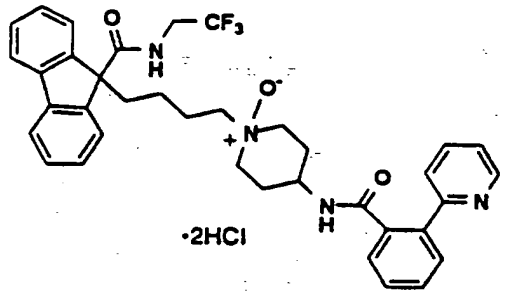
MS (electrospray, - ions) m/z 743 (M-H)

Elemental Anal. Calc'd for $C_{39}H_{36}ClF_6N_3O_3+0.88\ H_2O$:

C, 61.63; H, 5.01; N, 5.53; Cl, 4.66

Found: C, 61.64; H, 5.05; N, 5.42; Cl, 5.02

Example 64*



9-[4-[4-[(2-Pyridinylbenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide, dihydrochloride.

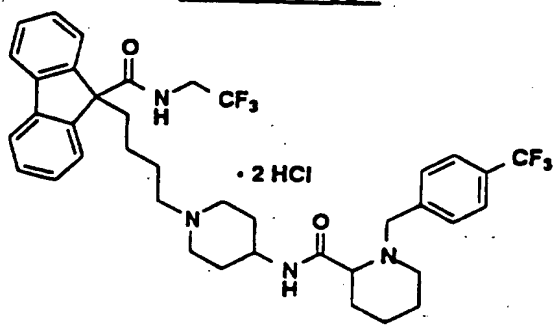
MS $(M+H)^+$ 643; $(M-H)^-$ 641

Elemental Anal. Calc'd for $C_{37}H_{37}F_3N_4O_3+2\ HCl + 1.94\ H_2O$:

C, 59.21; H, 5.76; N, 7.46; F, 7.59; Cl, 9.45

Found: C, 59.61; H, 5.81; N, 7.25; F, 7.19; Cl, 9.05

Example 65*



N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[1-[[4-(trifluoromethyl)phenyl]methyl]-2-piperidinyl]carbonyl]amino]-1-piperidinyl]butyl]-9*H*-fluorene-9-carboxamide,dihydrochloride.

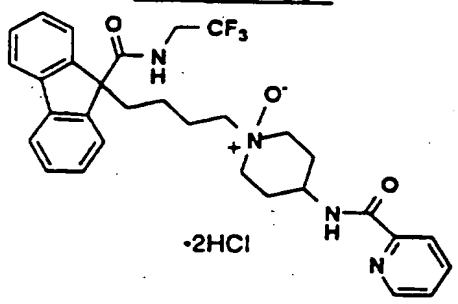
MS (ES, + ions) m/z 715 [M+H]

Elemental Anal. Calc'd for $C_{39}H_{44}F_6N_4O_2$+2 H_2O + 2 HCl:

C, 56.87; H, 6.12; N, 6.80

Found: C, 57.01; H, 6.01; N, 6.74

Example 66*



N-[1-[4-[9-[[(2,2,2-Trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]butyl]-4-piperidinyl]-2-pyridinecarboxamide, N-oxide, dihydrochloride.

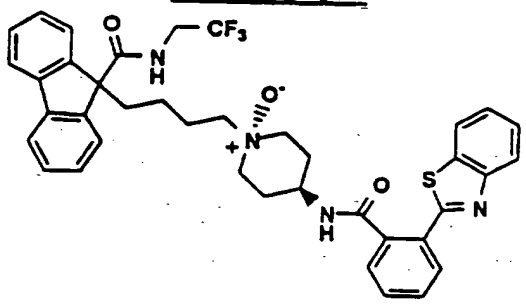
MS $(M+H)^+$ @ 567; $(M-H)^-$ @ 565; $(2M+H)^+$ @ 1133

Elemental Anal. Calc'd for $C_{31}H_{33}F_3N_4O_3$+2 HCl+1.7 H_2O:

C, 55.56; H, 5.78; N, 8.36; F, 8.50; Cl, 10.58

Found: C, 55.89; H, 5.81; N, 8.18; F, 8.66; Cl, 10.18

Example 67*



trans-9-[4-[4-[[2-(2-Benzothiazolyl)benzoyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide.

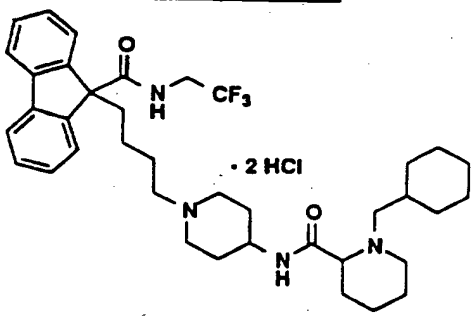
MS $(M+H)^+$ @ 699; $(M-H)^-$ @ 697

Elemental Anal. Calc'd for $C_{39}H_{37}F_3N_4O_3S+1.5\ H_2O+0.3\ C_6H_{14}$:

C, 65.19; H, 5.93; N, 7.45; F, 7.58; Cl, 4.27

Found: C, 65.12; H, 5.85; N, 7.29; F, 7.23; Cl, 4.29

Example 68*



9-[4-[4-[[[1-(Cyclohexylmethyl)-2-piperidinyl]carbonyl]amino]-1-piperidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, dihydrochloride.

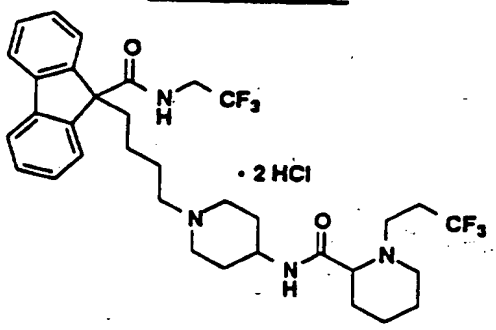
MS (ES, + ions) m/z 653 [M+H]

Elemental Anal. Calc'd for $C_{38}H_{53}Cl_2F_3N_4O_2+1.5\ H_2O$:

C, 60.63; H, 7.50; N, 7.44; F, 7.57; Cl, 9.42

Found: C, 60.73; H, 7.74; N, 7.65; F, 7.22; Cl, 9.85

Example 69*

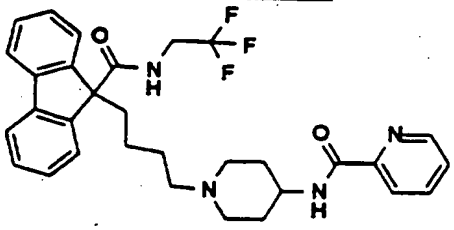


N-(2,2,2-Trifluoroethyl)-9-[4-[4-[[[1-(3,3,3-trifluoropropyl)-2-piperidinyl]carbonyl]amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, dihydrochloride.

MS (ES, + ions) m/z 653 [M+H]

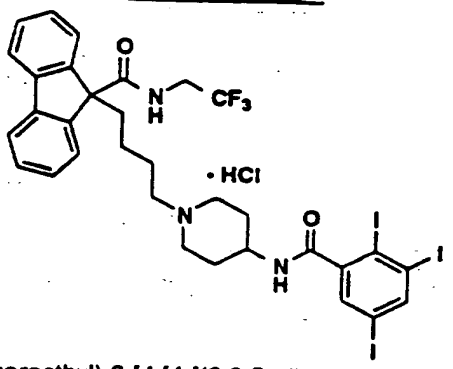
Elemental Anal. Calc'd for $C_{34}H_{44}Cl_2F_6N_4O_2+1.5\ H_2O$:
C, 54.26; H, 6.29; N, 7.44; F, 15.14
Found: C, 54.40; H, 6.21; N, 7.38; F, 15.53

Example 70*



MS (ESI + ions) m/z 551 (M+H)

Example 71*



N-(2,2,2-Trifluoroethyl)-9-[4-[4-[(2,3,5-triiodobenzoyl)amino]-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide, monohydrochloride.

M.P. 178-182°C

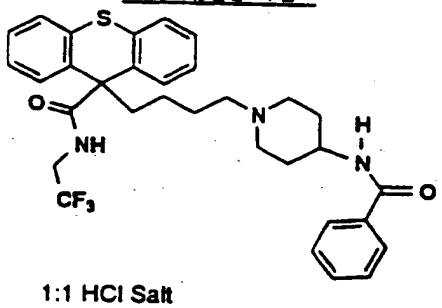
MS (ES, + ions) m/z 928 (M+H)

Elemental Anal. Calc'd for $C_{32}H_{32}ClF_3I_3N_3O_2$+0.5 H_2O:

C, 39.51; H, 3.42; N, 4.32; Cl, 3.64

Found: C, 39.40; H, 3.25; N, 4.27; Cl, 3.61

Example 72*



1:1 HCl Salt

9-[4-[4-(Benzoylamino)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide, monohydrochloride.

M.P. or B.P. 145-150°C

MS (ES, + ions) m/z 582 (M+H)

Elemental Anal. Calc'd for $C_{32}H_{34}N_3O_2F_3S$ + 1.0 HCl + 0.75 H_2O:

C, 60.94; H, 5.67; N, 6.66; F, 9.04

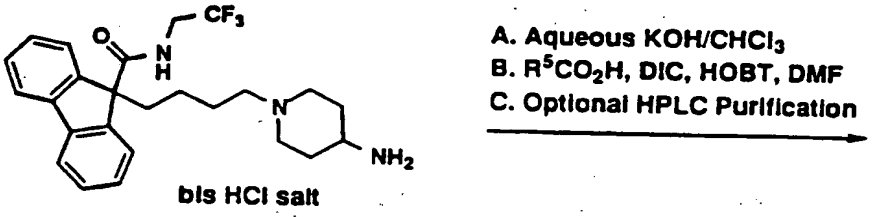
Found: C, 60.97; H, 6.00; N, 6.26; F, 9.15.

Examples 73* to 159*

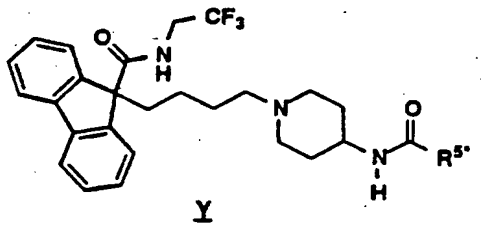
The following compounds were prepared by robotics procedures as described below.

ROBOTICS PROCEDURES

Robotic Method for the Preparation of Amides



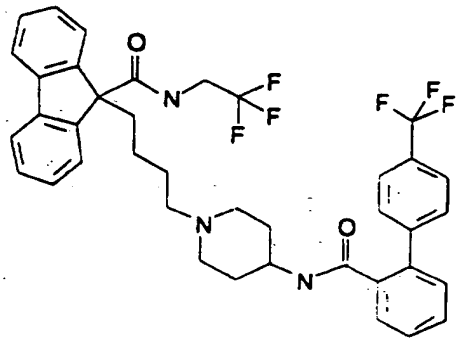
X
(Example 11 Part C)



Y

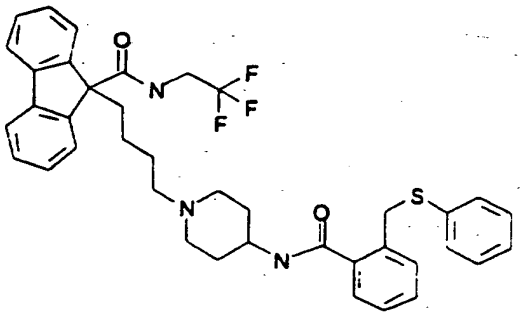
Please note that in the Examples 73* to 159*, for structures bearing only two single bonded substituents to nitrogen, the third substituent is always hydrogen, but it is not shown explicitly in the structures. Also, please note that in the Examples 73* to 159* for structures bearing oxygens and sulfurs with only one single bonded substituent, the second substituent is always hydrogen, but is not shown explicitly in the structures.

Example 73*



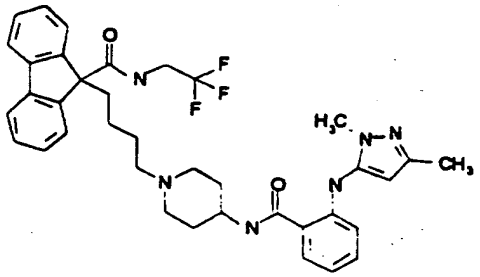
m/z 694 (M+H)

Example 74*



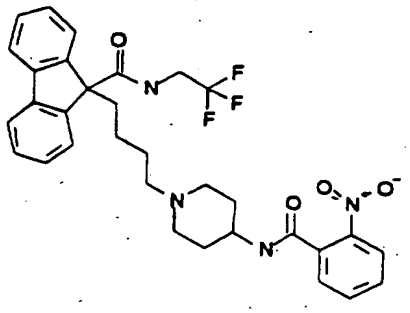
m/z 672 (M+H)

Example 75*



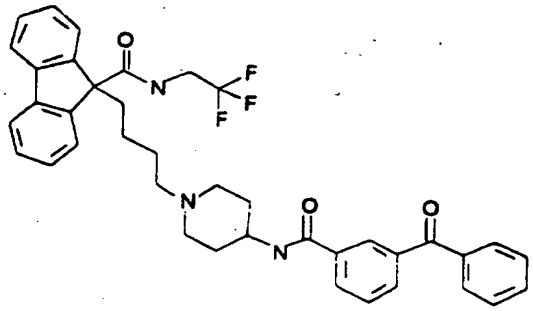
m/z 659 (M+H)

Example 76*



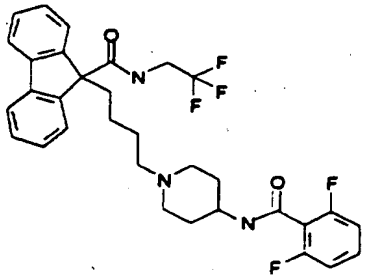
m/z 595 (M+H)

Example 77*



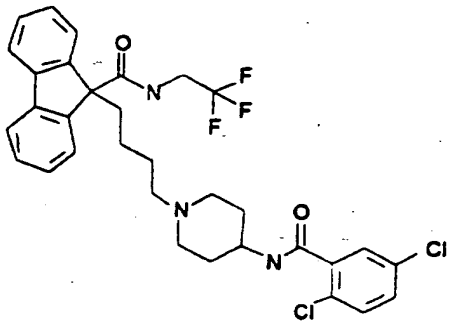
m/z 654 (M+H)

Example 78*



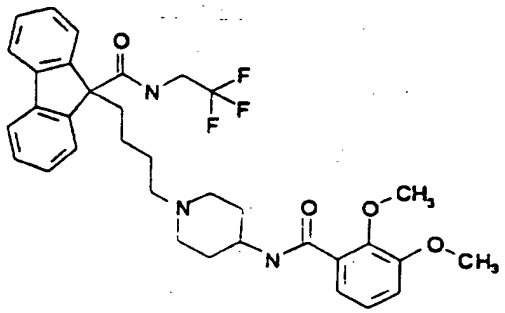
m/z 586 (M+H)

Example 79*



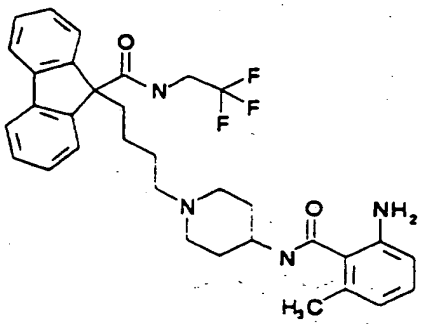
m/z 619 (M+H)

Example 80*



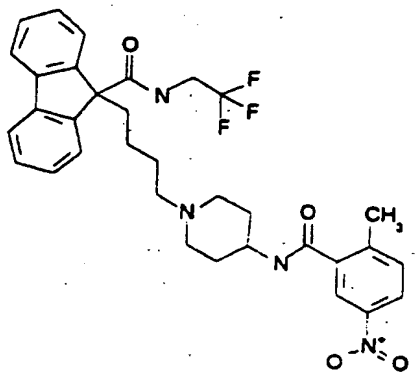
m/z 610 (M+H)

Example 81*



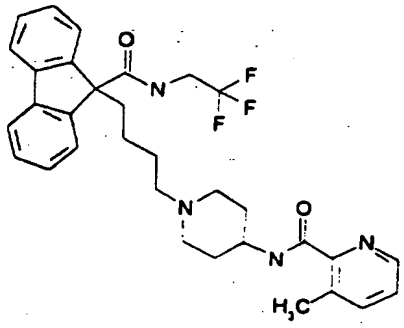
m/z 579 (M+H)

Example 82*



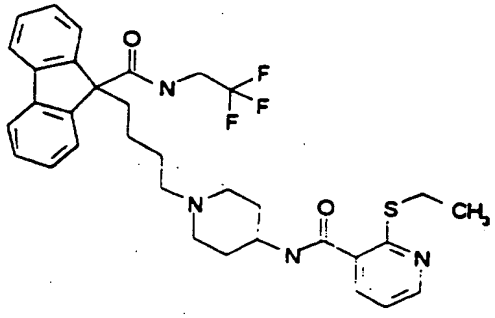
m/z 609 (M+H)

Example 83*



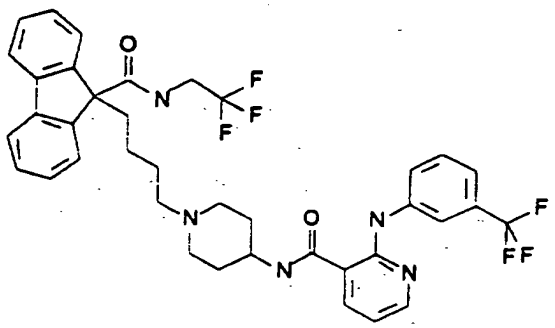
m/z 565 (M+H)

Example 84*



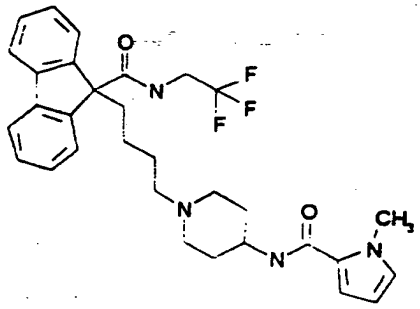
m/z 611 (M+H)

Example 85*



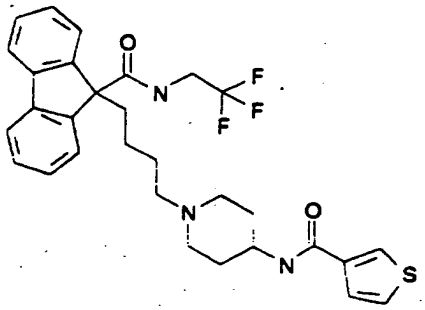
m/z 710 (M+H)

Example 86*



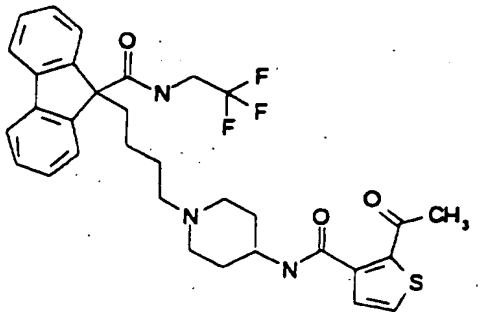
m/z 553 (M+H)

Example 87*



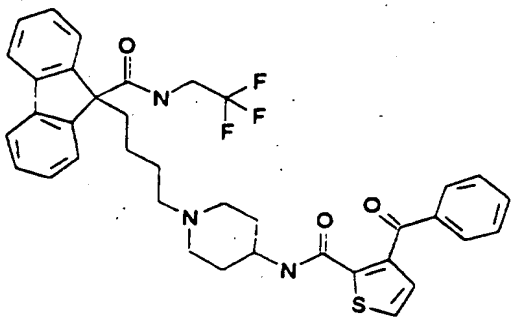
m/z 556 (M+H)

Example 88*



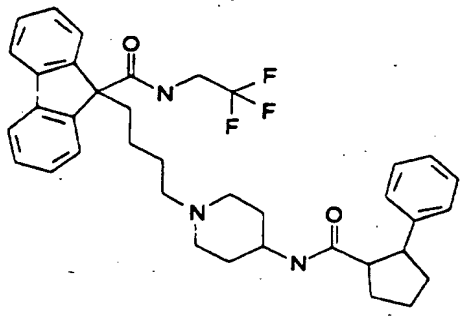
m/z 598 (M+H)

Example 89*



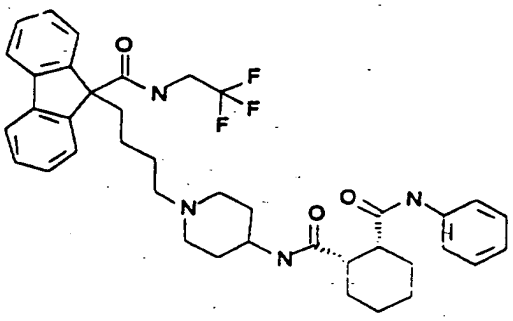
m/z 660 (M+H)

Example 90*



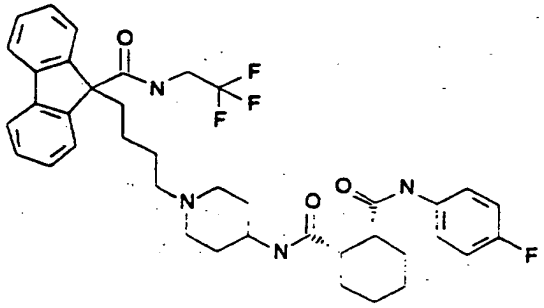
m/z 618 (M+H)

Example 91*



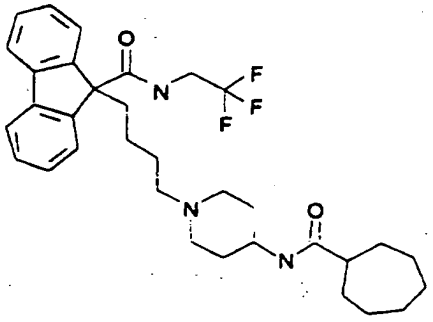
m/z 675 (M+H)

Example 92*



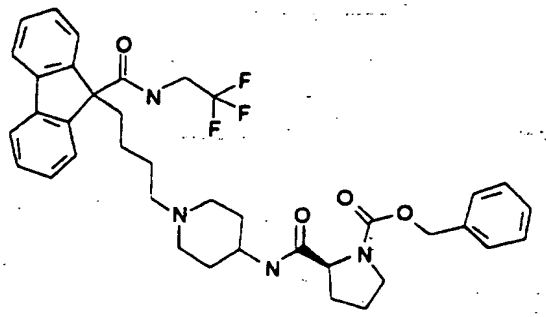
m/z 693 (M+H)

Example 93*



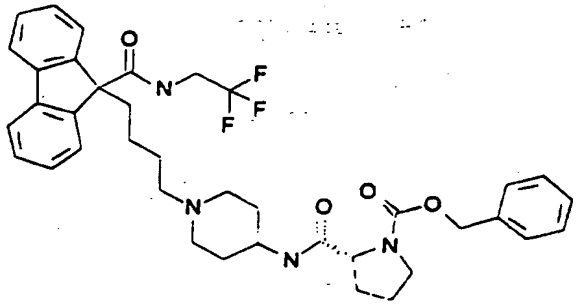
m/z 570 (M+H)

Example 94*



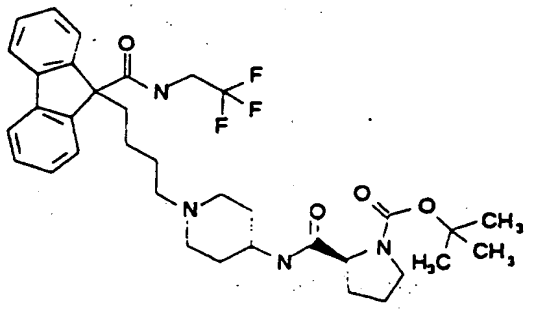
m/z 677 (M+H)

Example 95*



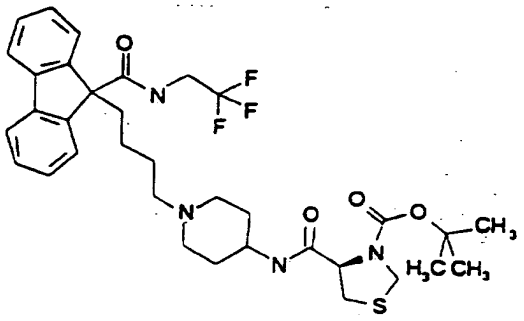
m/z 677 (M+H)

Example 96*



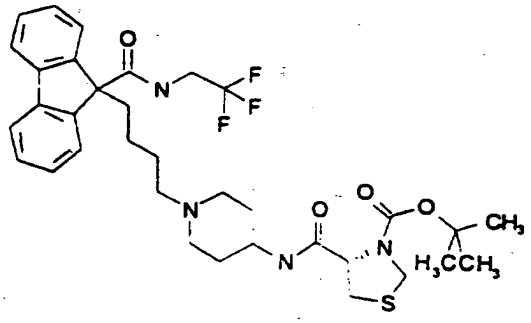
m/z 643 (M+H)

Example 97*



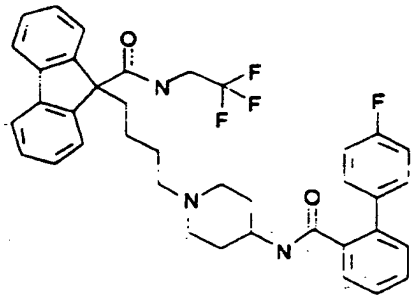
m/z 661 (M+H)

Example 98*



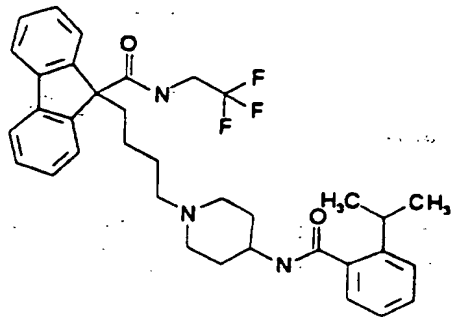
m/z 661 (M+H)

Example 99*



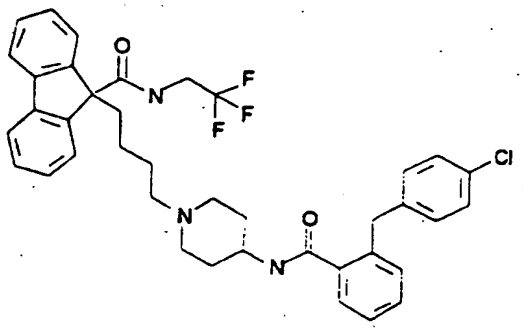
m/z 644 (M+H)

Example 100*



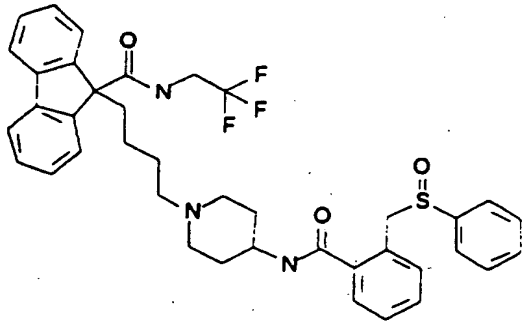
m/z 592 (M+H)

Example 101*



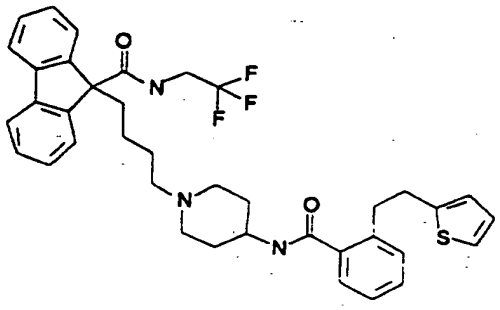
m/z 675 (M+H)

Example 102*



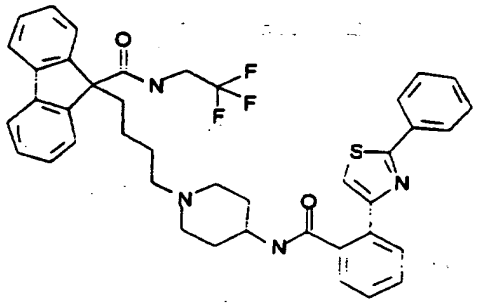
m/z 688 (M+H)

Example 103*



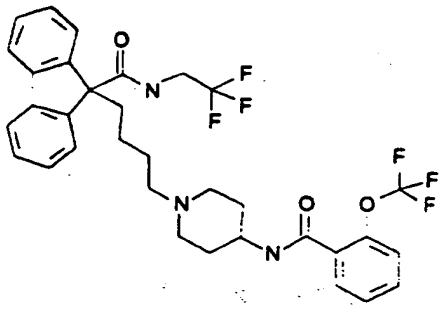
m/z 660 (M+H)

Example 104*



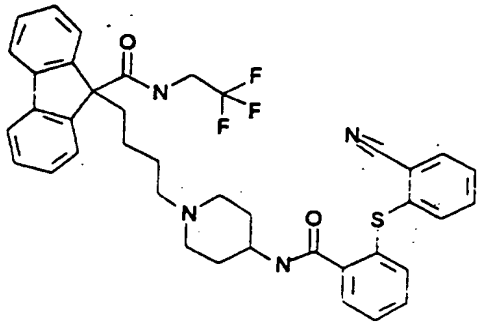
m/z 709 (M+H)

Example 105*



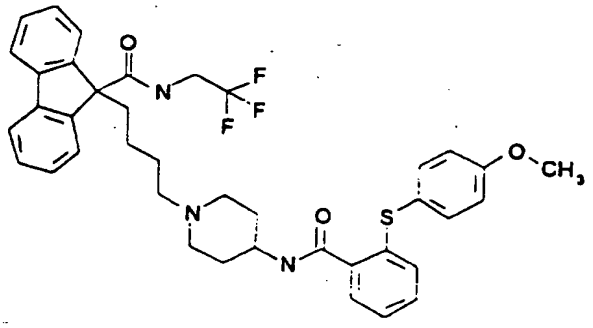
m/z 634 (M+H)

Example 106*



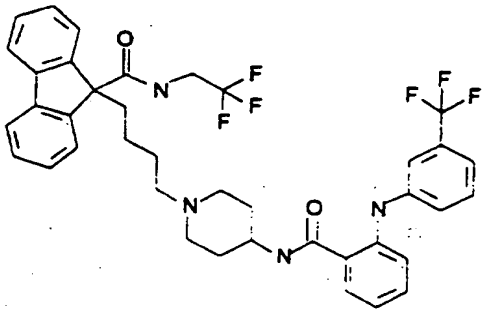
m/z 683 (M+H)

Example 107*



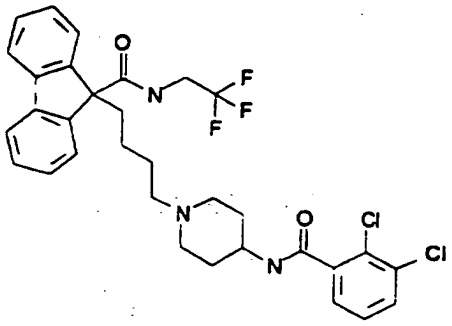
m/z 688 (M+H)

Example 108*



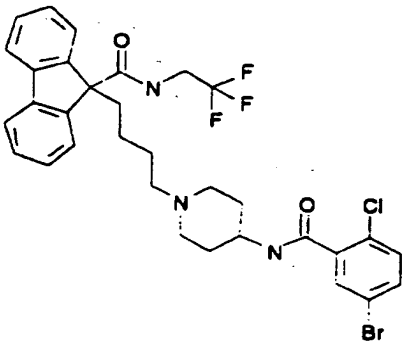
m/z 709 (M+H)

Example 109*



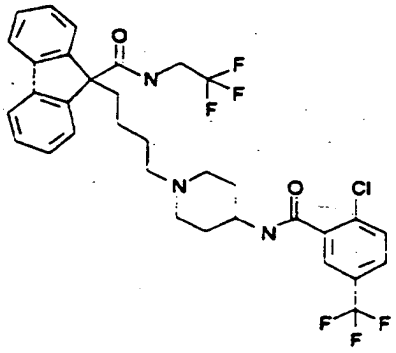
m/z 619 (M+H)

Example 110*



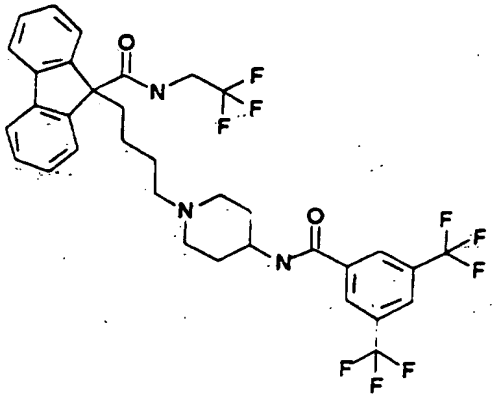
m/z 663 (M+H)

Example 111*



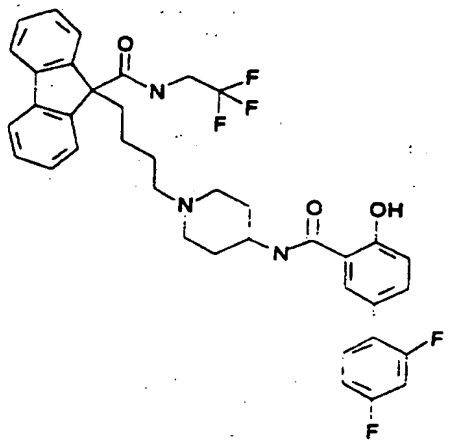
m/z 653 (M+H)

Example 112*



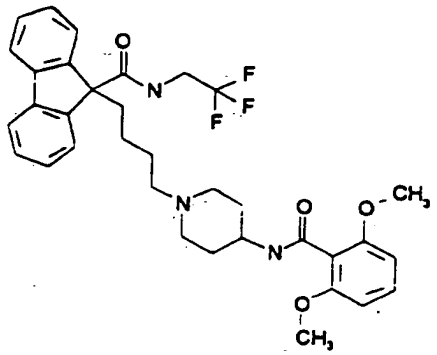
m/z 686 (M+H)

Example 113*



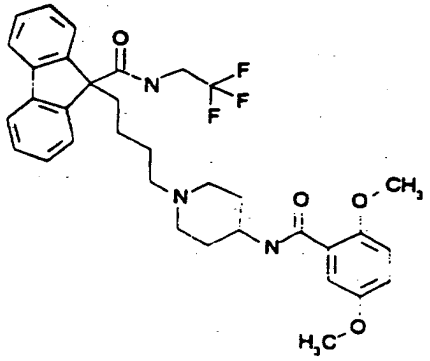
m/z 678 (M+H

Example 114*



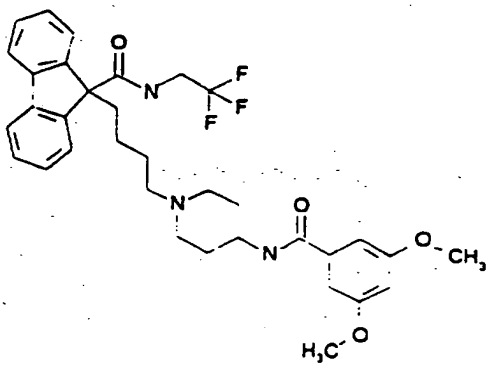
m/z 610 (M+H)

Example 115*



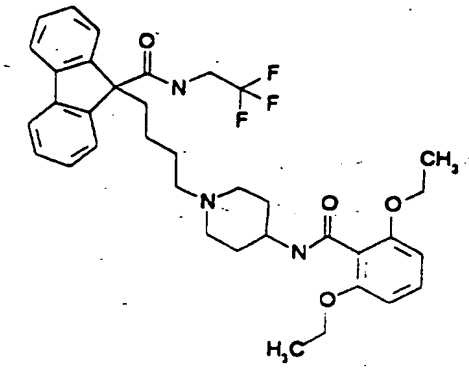
m/z 610 (M+H)

Example 116*



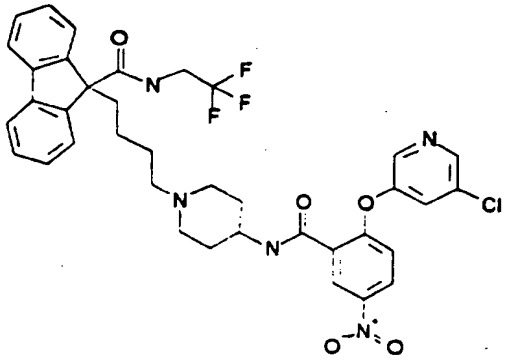
m/z 610 (M+H)

Example 117*



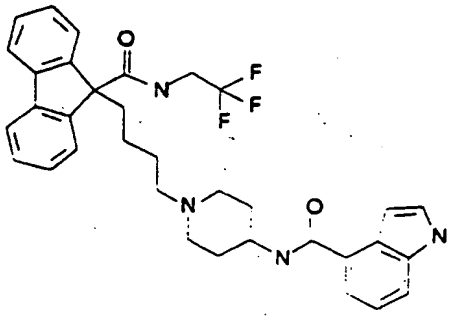
m/z 638 (M+H)

Example 118*



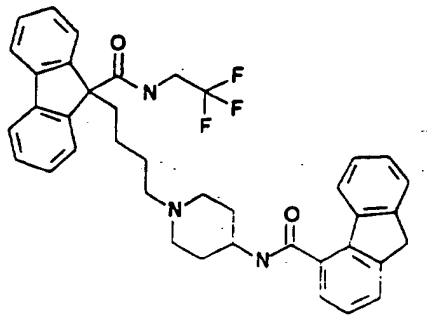
m/z 723 (M+H)

Example 119*



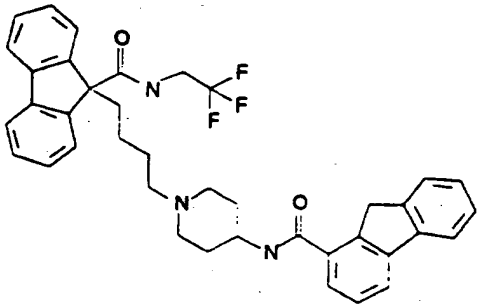
m/z 589 (M+H)

Example 120*



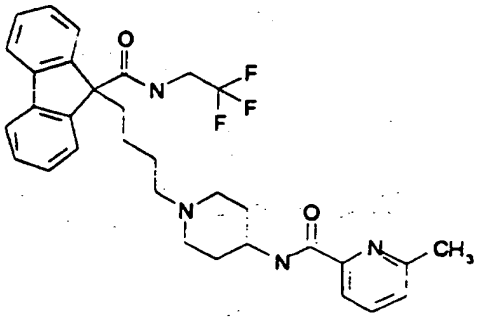
m/z 638 (M+H)

Example 121*



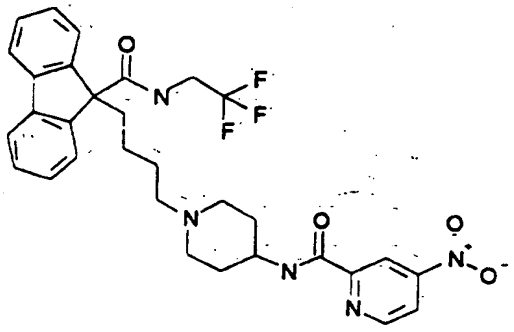
m/z 638 (M+H)

Example 122*



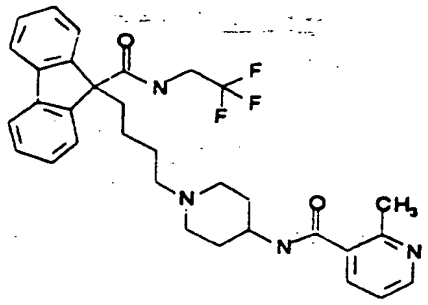
m/z 565 (M+H)

Example 123*



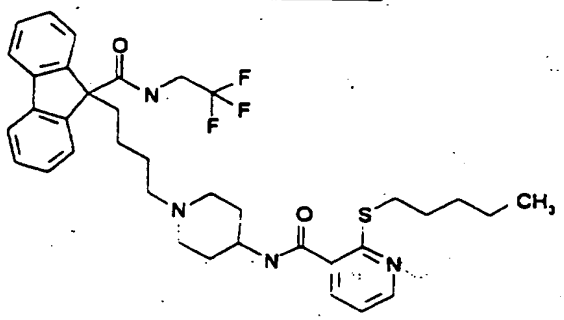
m/z 596 (M+H)

Example 124*



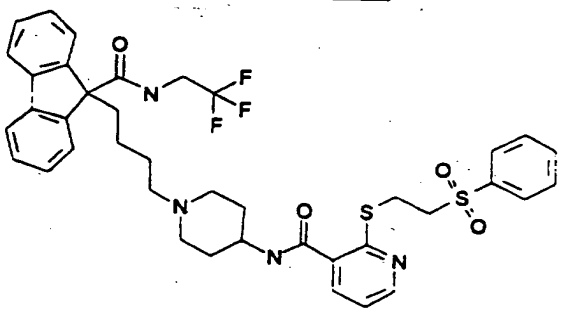
m/z 565 (M+H)

Example 125*



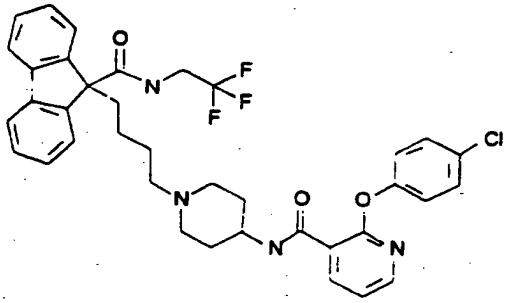
m/z 653 (M+H)

Example 126*



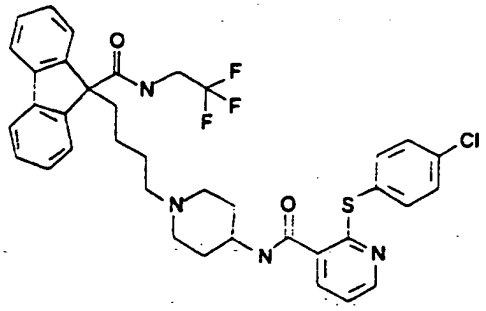
m/z 751 (M+H)

Example 127*



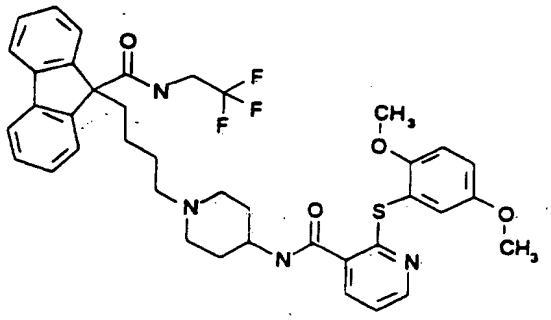
m/z 678 (M+H)

Example 128*



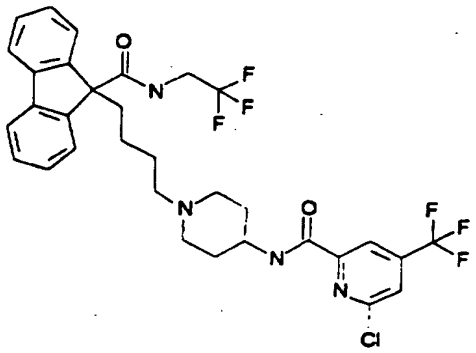
m/z 694 (M+H)

Example 129*



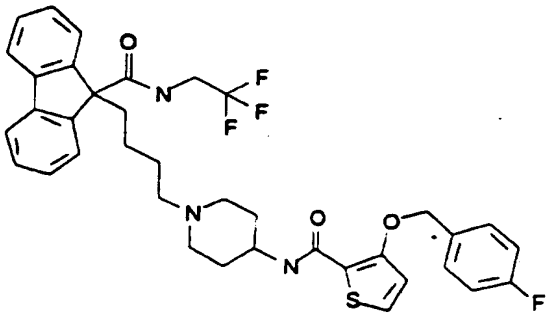
m/z 719 (M+H)

Example 130*



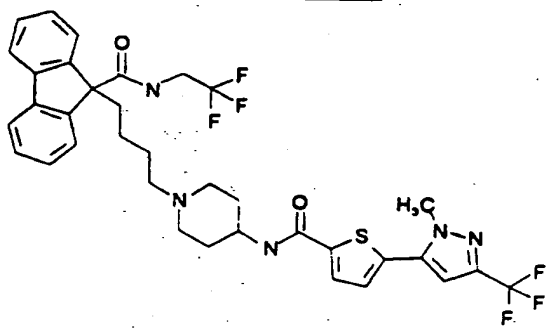
m/z 654 (M+H)

Example 131*



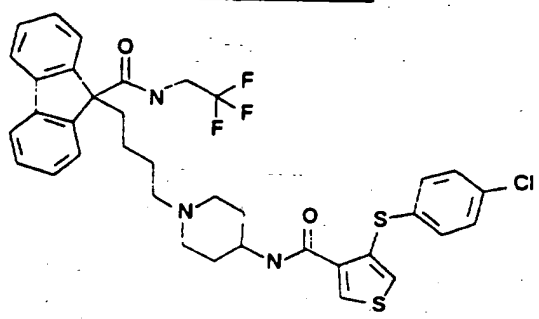
m/z 680 (M+H)

Example 132*



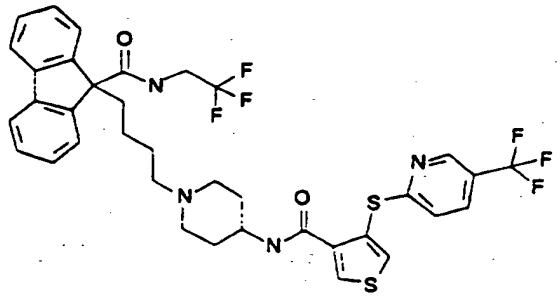
m/z 704 (M+H)

Example 133*



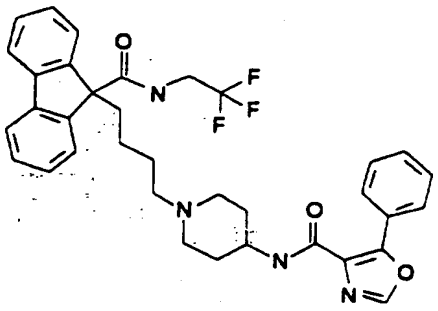
m/z 699 (M+H)

Example 134*



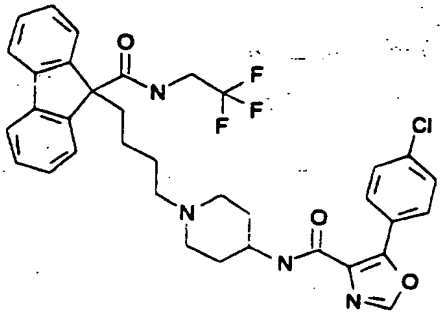
m/z 733 (M+H)

Example 135*



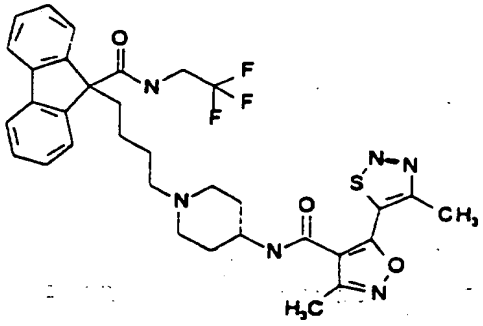
m/z 617 (M+H)

Example 136*



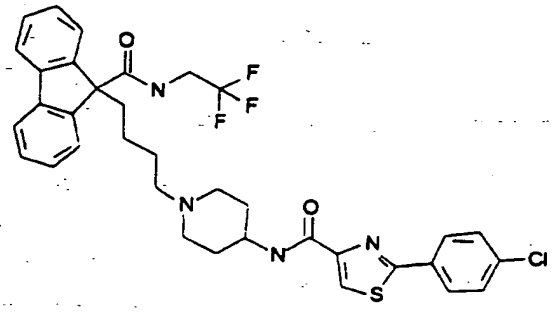
m/z 652 (M+H)

Example 137*



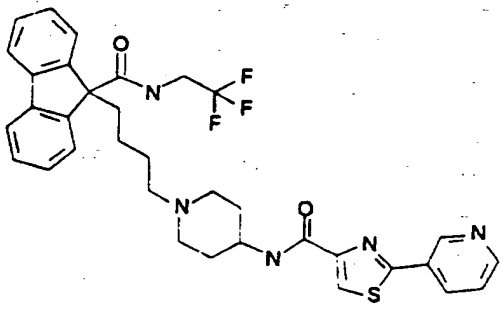
m/z 653 (M+H)

Example 138*



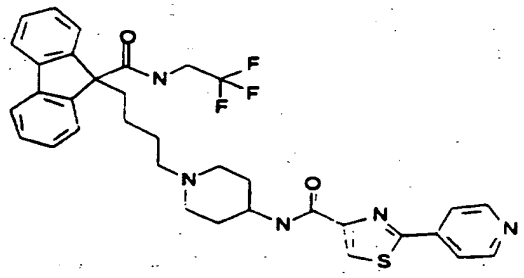
m/z 668 (M+H)

Example 139*



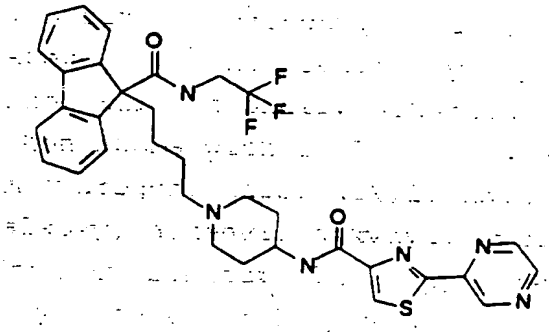
m/z 634 (M+H)

Example 140*



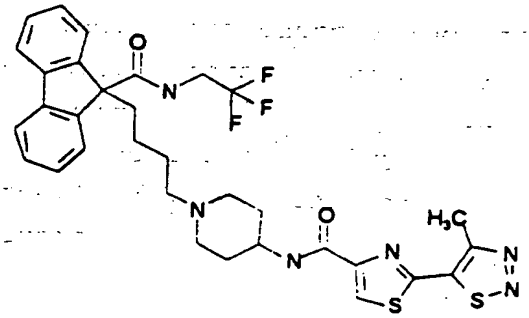
m/z 634 (M+H)

Example 141*



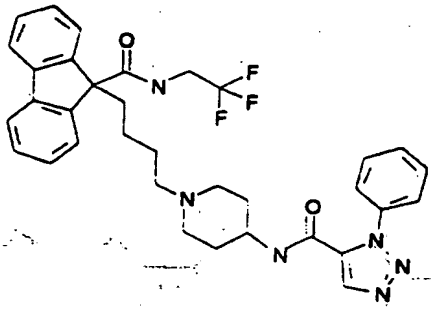
m/z 635 (M+H)

Example 142*



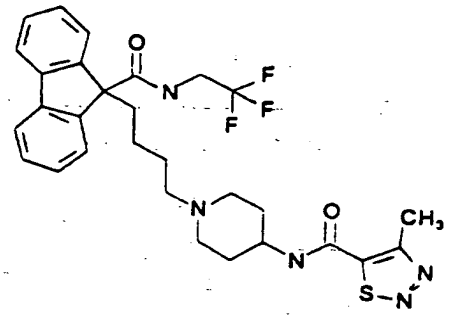
m/z 655 (M+H)

Example 143*



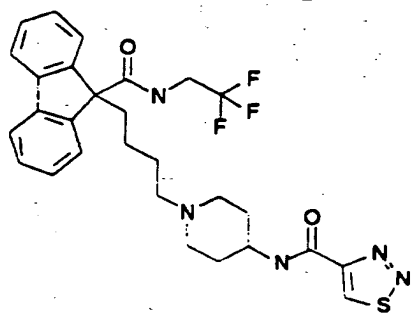
m/z 617 (M+H)

Example 144*



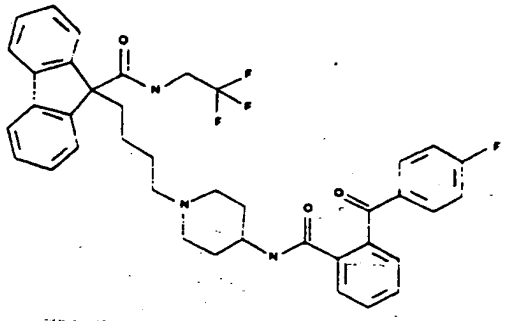
m/z 572 (M+H)

Example 145*



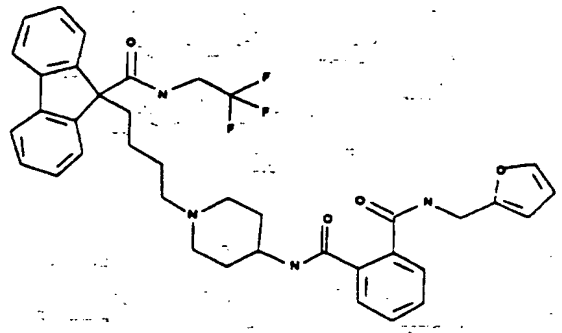
m/z 558 (M+H)

Example 146*



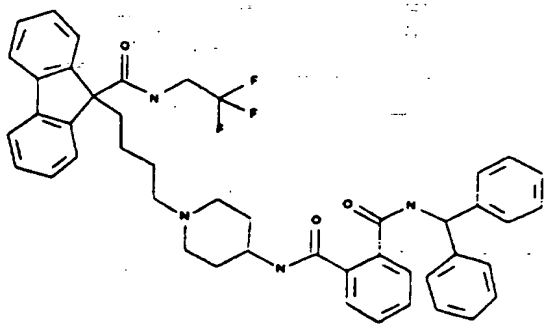
m/z 672 (M+H)

Example 147*



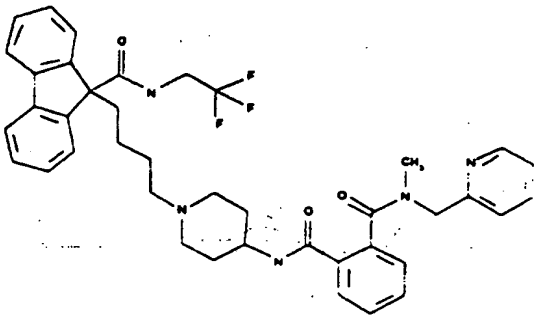
m/z 673 (M+H)

Example 148*



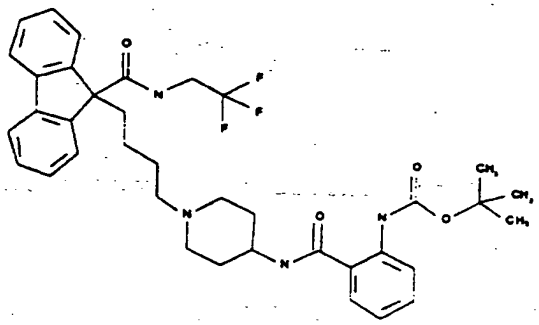
m/z 759 (M+H)

Example 149*



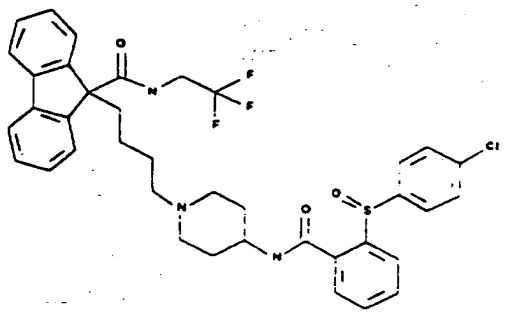
m/z 698 (M+H)

Example 150*



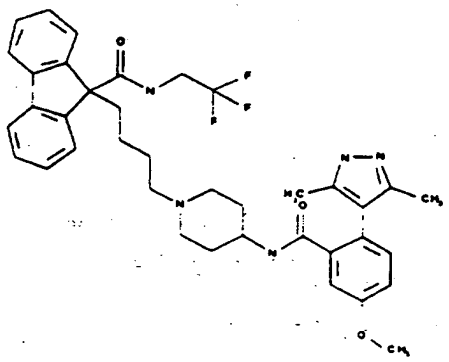
m/z 665 (M+H)

Example 151*



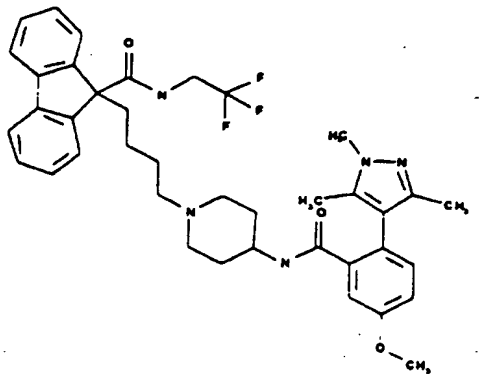
m/z 709 (M+H)

Example 152*



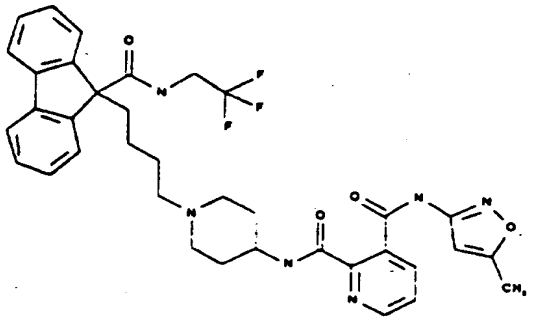
m/z 674 (M+H)

Example 153*



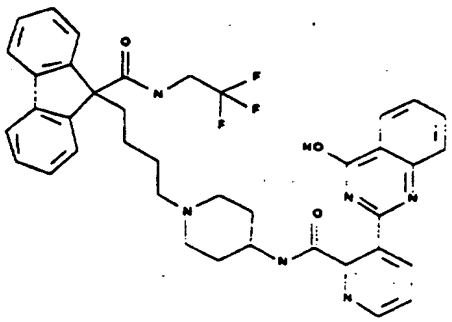
m/z 688 (M+H)

Example 154*



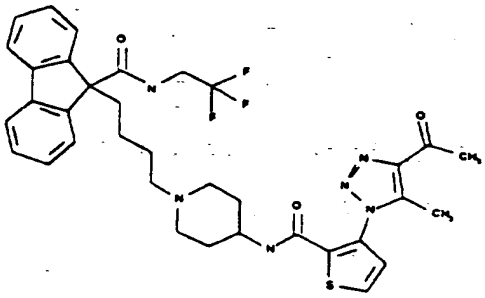
m/z 675 (M+H)

Example 155*



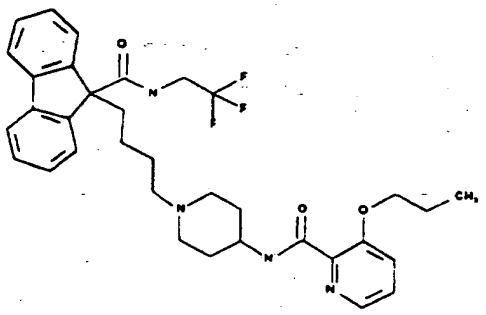
m/z 695 (M+H)

Example 156*



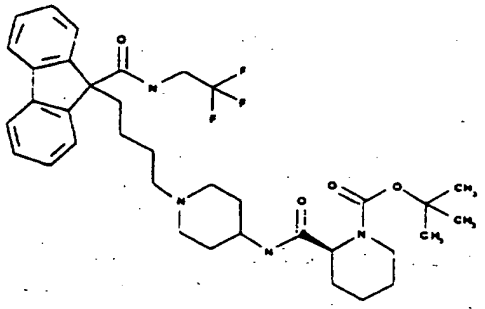
m/z 679 (M+H)

Example 157*



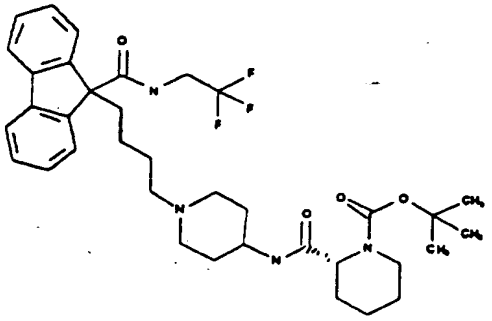
m/z 609 (M+H)

Example 158*



m/z 657 (M+H)

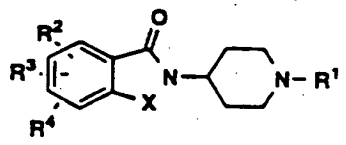
Example 159*



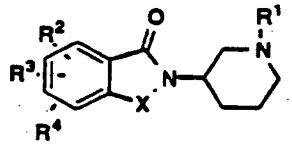
m/z 657 (M+H)

What We Claimed Is:

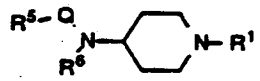
1. A compound which has the structure



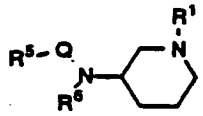
or



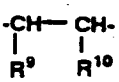
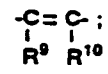
or



or

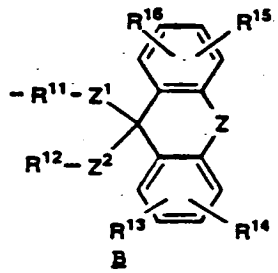


where Q is  or  ;

X is: CHR^8,  ,  or  ;

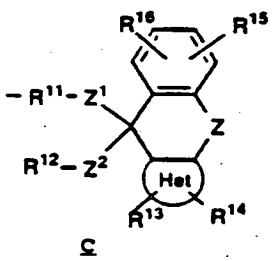
R^8, R^9 and R^{10} are independently hydrogen, alkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, cycloalkyl, or cycloalkylalkyl;

R^1 is a fluorenyl-type group of the structure

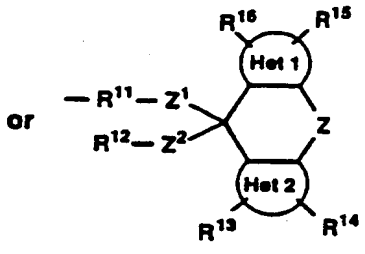


B

or



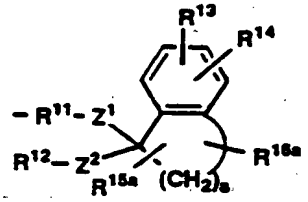
C



; or

D

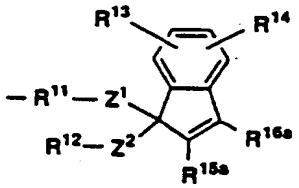
R^1 is an indenyl-type group of the structure



E

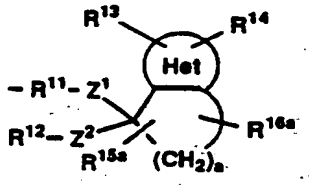
(a = 2,3 or 4)

or



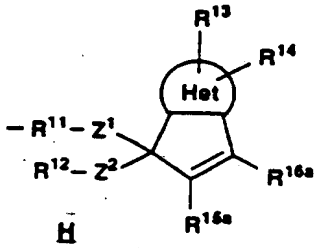
or

F



G

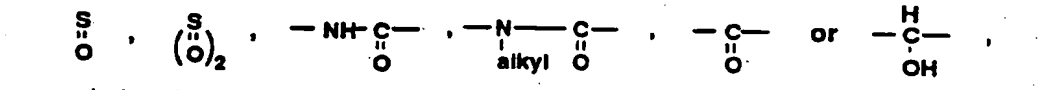
or



;

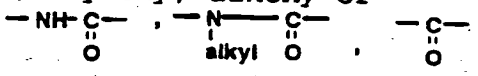
H

Z^1 and Z^2 are the same or different and are independently a bond, O, S,



with the proviso that with respect to B, at least one of Z^1 and Z^2 will be other than a bond; R^{11} is a bond, alkylene, alkenylene or alkynylene of up to 10 carbon atoms; arylene or mixed arylenealkylene; R^{12} is hydrogen, alkyl, alkenyl, aryl, haloalkyl, trihaloalkyl, trihaloalkylalkyl, heteroaryl, heteroaryl-

alkyl, arylalkyl, arylalkenyl, cycloalkyl, aryloxy, alkoxy, arylalkoxy or cycloalkylalkyl, with the provisos that

(1) when R^{12} is H, aryloxy, alkoxy or arylalkoxy, then Z^2 is  or a bond and

(2) when Z^2 is a bond, R^{12} cannot be heteroaryl or heteroarylalkyl;

Z is bond, O, S, N-alkyl, N-aryl, or alkylene or alkenylene from 1 to 5 carbon atoms; R^{13}, R^{14}, R^{15}, and R^{16} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, hydroxy, alkoxy, nitro, amino, thio, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl or aryloxy;

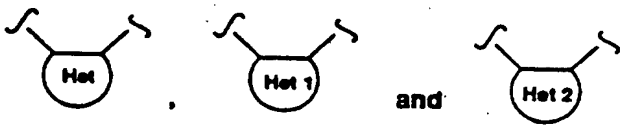
R^{15a} and R^{16a} are independently hydrogen, alkyl, halo, haloalkyl, aryl, cycloalkyl, cycloheteroalkyl, alkenyl, alkynyl, alkoxy, alkylsulfonyl, arylsulfonyl, alkylthio, arylthio, aminocarbonyl, alkylcarbonyloxy, arylcarbonylamino, alkylcarbonylamino, arylalkyl, heteroaryl, heteroarylalkyl, or aryloxy;

R^2, R^3, R^4 are independently hydrogen, halo, alkyl, alkenyl, alkoxy, aryloxy, aryl, arylalkyl, alkylmercapto, arylmercapto, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroarylalkyl, hydroxy or haloalkyl;

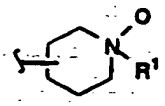
R^5 is independently alkyl, alkenyl, alkynyl, aryl, alkoxy, aryloxy, arylalkoxy, heteroaryl, arylalkyl, heteroarylalkyl, cycloalkyl, cycloalkylalkyl, polycycloalkyl, polycycloalkylalkyl, cycloalkenyl, cycloheteroalkyl, heteroaryloxy,

cycloalkenylalkyl, polycycloalkenyl, polycycloalkenylalkyl, heteroarylcarbonyl, amino, alkylamino, arylamino, heteroarylamino, cycloalkyloxy, cycloalkylamino, all optionally substituted through available carbon atoms with 1, 2, 3 or 4 groups selected from hydrogen, halo, alkyl, haloalkyl, alkoxy, haloalkoxy, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, cycloheteroalkyl, cycloheteroalkylalkyl, aryl, heteroaryl, arylalkyl, arylcycloalkyl, arylalkenyl, arylalkynyl, aryloxy, aryloxyalkyl, arylalkoxy, arylazo, heteroaryloxo, heteroarylalkyl, heteroarylalkenyl, heteroaryloxy, hydroxy, nitro, cyano, amino, substituted amino, thiol, alkylthio, arylthio, heteroarylthio, arylthioalkyl, alkylcarbonyl, arylcarbonyl, arylaminocarbonyl, alkoxycarbonyl, aminocarbonyl, alkynylaminocarbonyl, alkylaminocarbonyl, alkenylaminocarbonyl, alkylcarbonyloxy, arylcarbonyloxy, alkylcarbonylamino, arylcarbonylamino, arylsulfinyl, arylsulfinylalkyl, arylsulfonyl, alkylsulfonyl, arylsulfonylamino, heteroarylcarbonylamino, heteroarylsulfinyl, heteroarylthio, heteroarylsulfonyl, alkylsulfinyl;

R^6 is hydrogen or C_1-C_4 alkyl or C_1-C_4 alkenyl; all optionally substituted with 1, 2, 3 or 4 groups which may independently be any of the substituents listed in the definition of R^5 set out above;

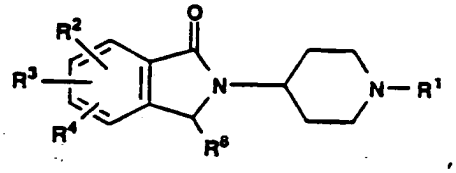


are the same or different and are independently selected from heteroaryl containing 5- or 6-ring members; and

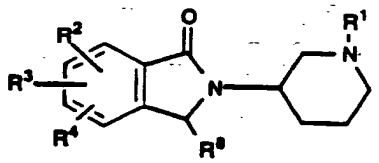


N-oxides thereof; and pharmaceutically acceptable salts thereof.

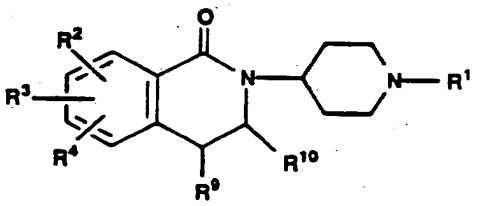
2. The compound as defined in Claim 1 having the formula



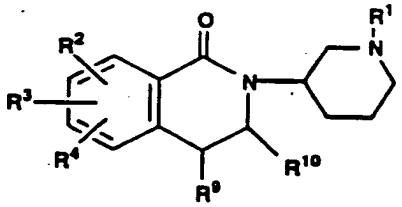
or



or



or



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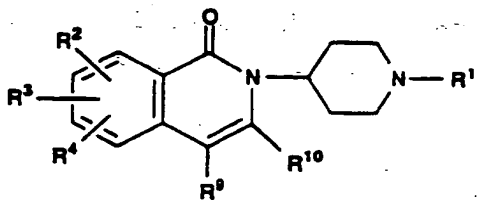

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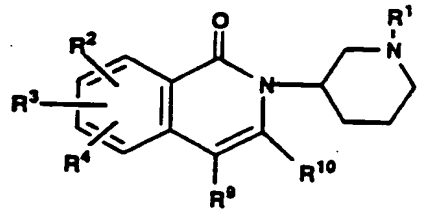

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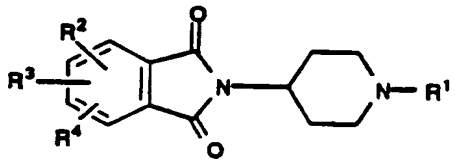

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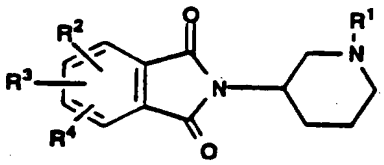
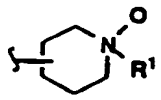
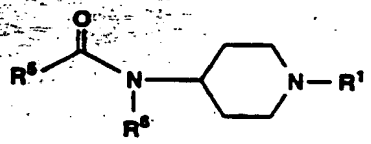




the N-oxides thereof and pharmaceutically acceptable salts thereof.

3. The compound as defined in Claim 1 having the formula



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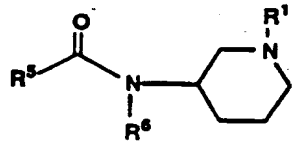

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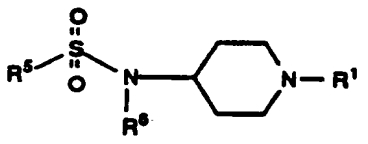

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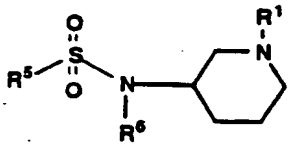
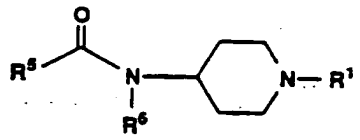
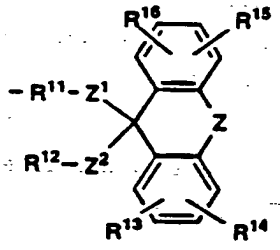


4. The compound as defined in Claim 1 having the formula

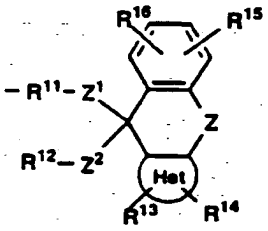


5. The compound as defined in Claim 1 wherein R^1 is



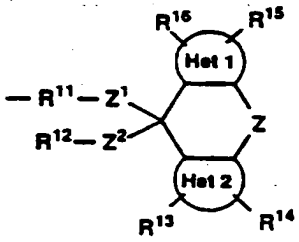
B

or



C

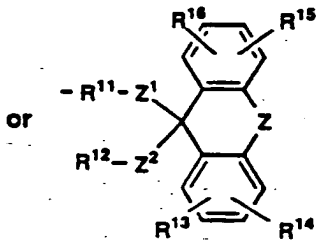
or



D

6. The compound as defined in Claim 5 wherein R^1 is

or



B

Z is a bond, O or S;

R^{13}, R^{14}, R^{15} and R^{16} are each H or one of R^{15} and R^{16} and one of R^{13} and R^{14} are halogen;

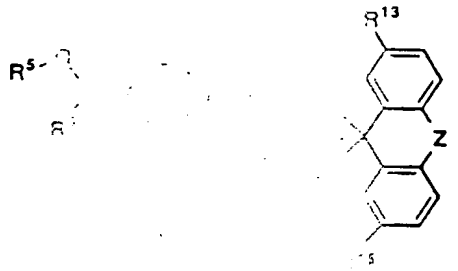
Z^1 is a bond [illegible],

R^{11} is alkyl [illegible] or alkenylene;

R^{12} - Z^2 is $R^{12a}-NH-\overset{O}{\overset{\|}{C}}-$; or $R^{12a}\overset{O}{\overset{\|}{C}}-$;

R^{12a} is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl.

7. The compound as defined in Claim 1 having the structrure



where Q is $-\overset{O}{\overset{\|}{C}}-$ or

Z is a bond

where R^5 is [illegible]yl, aryl, heteroaryl, or cyc[illegible] aryl or heteroaryl, indepen[illegible]ed at the ortho position with alky[illegible]kyl (optionally substituted with u[illegible] trifluoromethyl, aryl, aryloxy, hal[illegible]y substituted with up to 5 halog[illegible] arylalkoxy;

R^6 is H or

R^{13} and R^{15} [illegible] H or F;

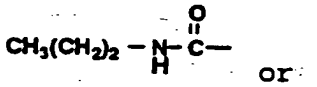
Z^1 is a bon[illegible]

R^{11} is alky[illegible]

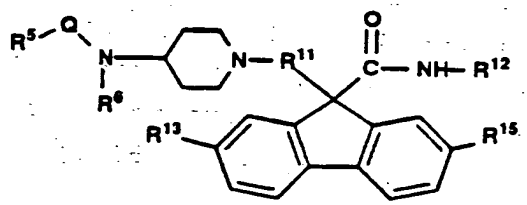
R^{12} - Z^2 is [illegible]alkylNHC$\overset{O}{\overset{\|}{}}$-,

or Z^2 is a [illegible]kyl.

8. The compound as defined in Claim 7 wherein R^{11} is $-(CH_2)_4-$, Z^1 is a bond, and $R^{12}-Z^2$ is

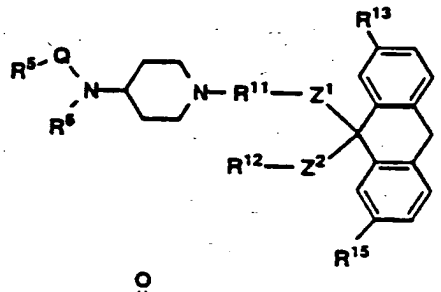


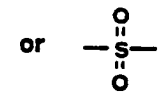
9. The compound as defined in Claim 7 having the structure



and R^{12} is trifluoromethylalkyl or alkyl.

10. The compound as defined in Claim 1 having the structrure



where Q is  or  ;

Z is a bond, O or S;

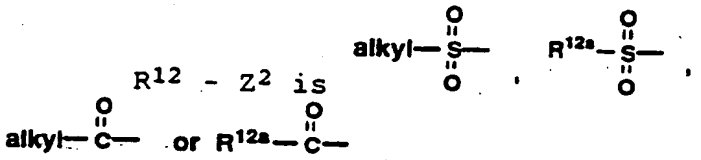
where R^5 is cycloalkyl, phenyl, aryl, heteroaryl, or cycloalkyl, phenyl, aryl or heteroaryl, independently substituted at the ortho position with alkyl, alkoxy, haloalkyl (optionally substituted with up to 5 halogens), trifluoromethyl, aryl, aryloxy, haloalkoxy (optionally substituted with up to 5 halogens), arylalkyl or arylalkoxy;

R^6 is H or CH_3;

R^{13} and R^{15} are independently H or F;

Z^1 is a bond;

R^{11} is alkylene;

R^{12} - Z^2 is 

R^{12a} is alkyl, fluorinated lower alkyl or polyfluorinated lower alkyl,

or Z^2 is a bond and R^{12} is alkyl.

11. The compound as defined in Claim 1 which is:

9-[3-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-propyl]-N-propyl-9H-fluorene-9-carboxamide;

2,3-dihydro-2-[1-[4-oxo-4-(9-propyl-9H-fluoren-9-yl)butyl]-4-piperidinyl]-1H-isoindol-1-one or its monohydrochloride salt;

(E)-9-[4-[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]-2-butenyl-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

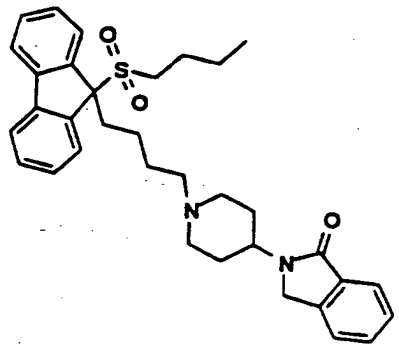
9-[4-[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-1-piper-idinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

(Z)-9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide;

2,3-dihydro-2-[1-[2-oxo-2-(9-propyl-9H-fluoren-9-yl)ethyl]-4-piperidinyl]-1H-isoindol-1-one;

(E)-9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-2-butenyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[3-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-propyl]-N-propyl-9H-fluorene-9-carboxamide;



;

9-[4-[4-[[(1,1-dimethylethoxy)carbonyl]-amino]-1-piper-idinyl]-butyl]-N-propyl-9H-fluorene-9-carboxamide;

N-[2-[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]-ethyl]-9-propyl-9H-fluorene-9-carboxamide;

9-[4-[4-[[2-(phenoxyphenyl)carbonyl]amino]-1-piperidinyl]-butyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[5-[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]-pentyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[4-[4-(benzoylamino)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[2-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-ethyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[4-[4-(acetylamino)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide;

N-ethyl-9-[4-[(4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-9H-fluorene-9-carboxamide;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-2,2,2-trifluoroethyl-9H-xanthene-9-carboxamide;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-butyl]-N-propyl-9H-xanthene-9-carboxamide;

9-[4-[4-(2,3-dihydro-1,3-dioxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]-butyl]-N-propyl-9H-indeno[2,1-b]pyridine-9-carboxamide;

2,3-dihydro-2-[1-[4-hydroxy-4-(9-propyl-9H-fluoren-9-yl)butyl]-4-piperidinyl]-1H-isoindol-1-one;

2,3-dihydro-2-[1-[3-[(9-propyl-9H-fluoren-9-yl)thio]propyl]-4-piperidinyl]-1H-isoindol-1-one;

2,3-dihydro-2-[1-[3-[(9-propyl-9H-fluoren-9-yl)sulfonyl]propyl]-4-piperidinyl]-1H-isoindol-1-one;

cis-9-[4-[4-(2,3-dihydro-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide;

2,3-dihydro-1-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-1H-indene-1-carboxamide;

trans-2,3-dihydro-1-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-2-phenyl-N-propyl-1H-indene-1-carboxamide;

1-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-2-phenyl-N-propyl-1H-indene-1-carboxamide;

2-[1-[4-[9-(butylsulfonyl)-9H-fluoren-9-yl]butyl]-4-piperidinyl]-2,3-dihydro-1H-isoindol-1-one;

9-[4-[[4-[(1,1-dimethylethoxy)carbonyl]-amino]-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[4-[4-[(2-phenoxybenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[4-[[4-(benzoylamino)-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[4-[[4-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-2,7-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

2,7-difluoro-9-[4-[[4-[(2-phenoxybenzolyl)-amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoro-ethyl)-9H-fluorene-9-carboxamide;

9-[4-[4-(benzoylamino)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

2,3-dihydro-2-[1-[4-[9-(1-oxopentyl)-9H-fluoren-9-yl]butyl]-4-piperidinyl]-1H-isoindol-1-one;

2,3-dihydro-2-[1-(1-oxo-3,3-diphenylpropyl)-4-piperidinyl]-1H-isoindol-1-one;

[1-[4-[9-[(propylamino)carbonyl]-9H-fluoren-9-yl]butyl]-3-piperidinyl]carbamic acid, phenylmethyl ester;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[4-[3-(benzoylamino)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[4-[3-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-N-propyl-9H-fluorene-9-carboxamide;

9-[4-[4-(2,3-dihydro-1-oxo-1H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,3,3,4,4,4-heptafluorobutyl)-9H-fluorene-9-carboxamide;

9-[4-[[4-[(1,1-dimethylethoxy)carbonyl]amino]-1-piperidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

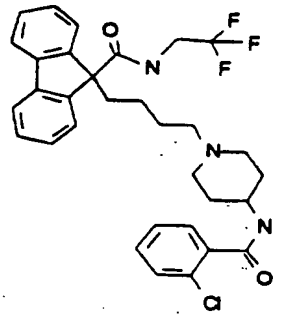
1-[4-[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-2-methyl-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide;

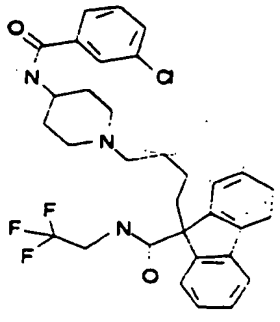
9-[4-[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,3,3,3-pentafluoropropyl)-9H-fluorene-9-carboxamide;

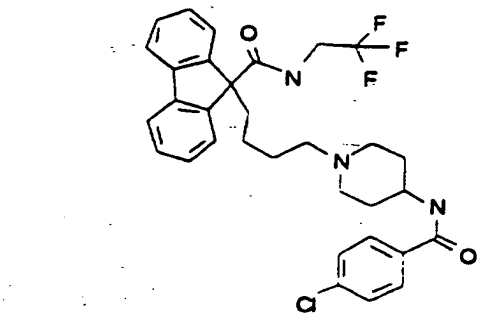
1-[4-[4-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-1H-indene-1-carboxamide;

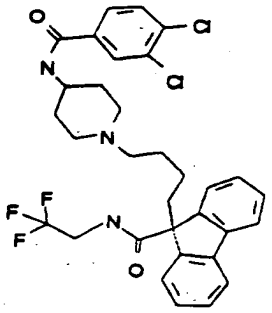
9-[4-[4-(benzoylamino)-1-piperidinyl]butyl]-3,6-difluoro-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

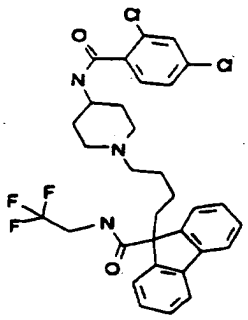
3,6-difluoro-9-[4-[4-[(2-phenoxybenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

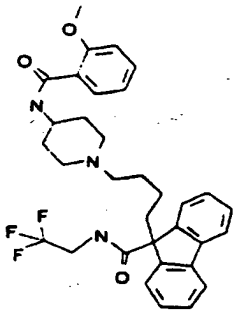


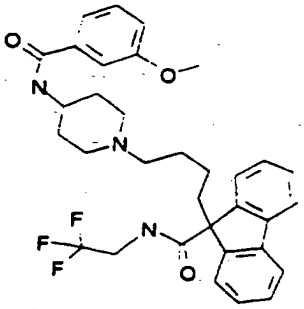


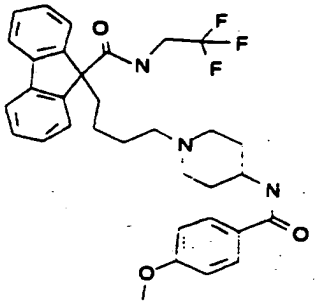


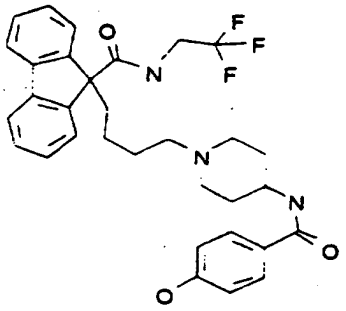


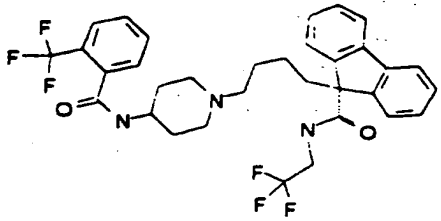


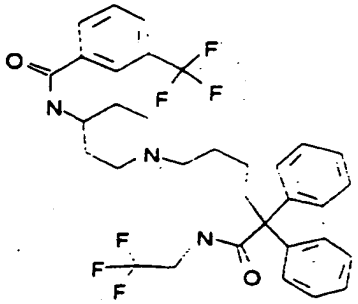












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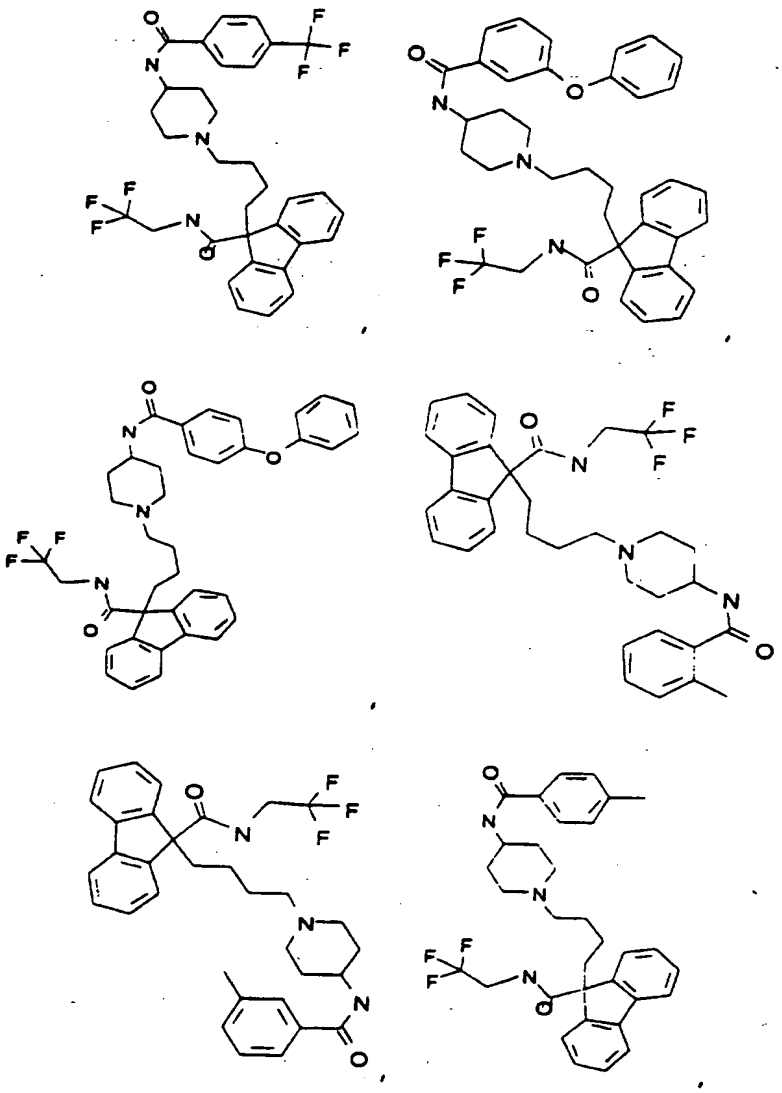

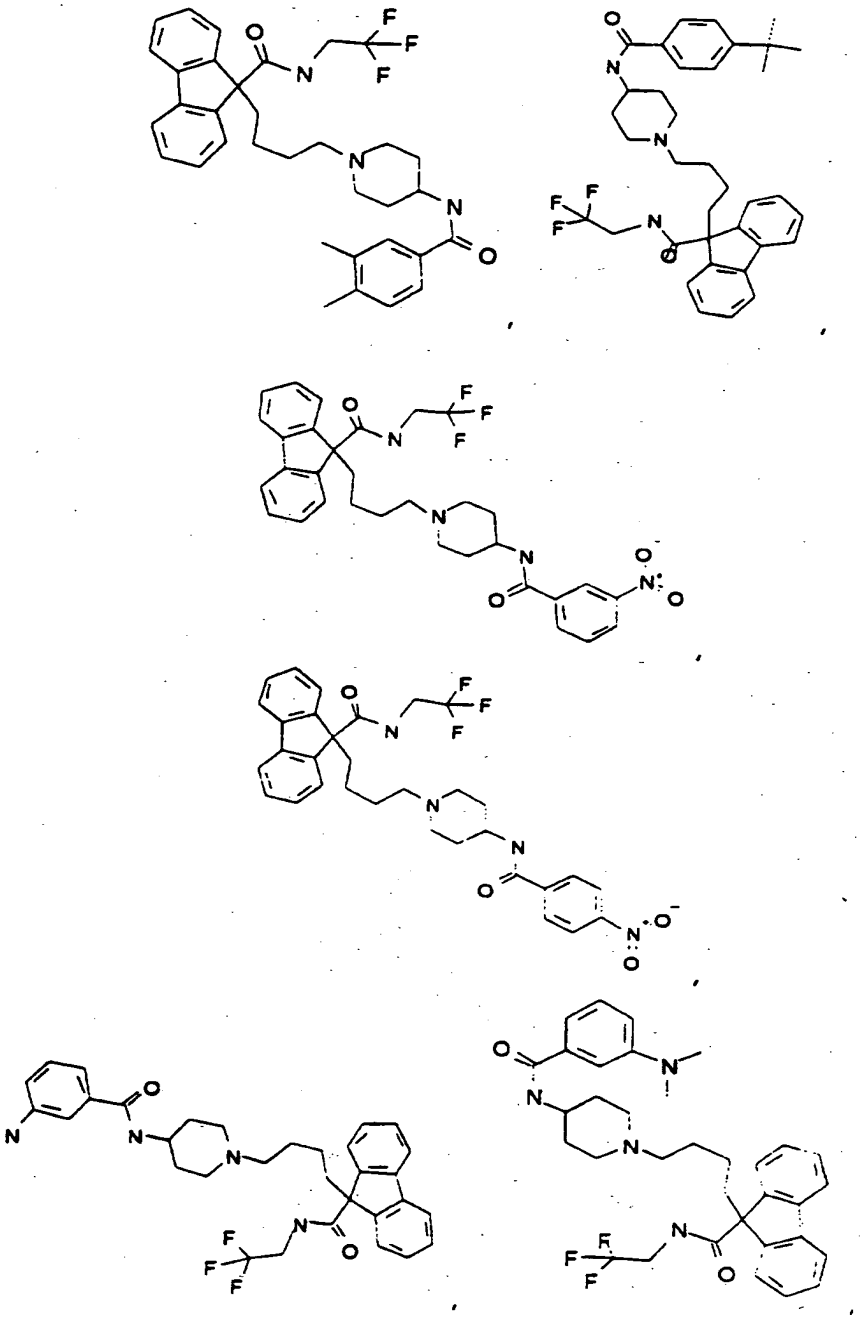

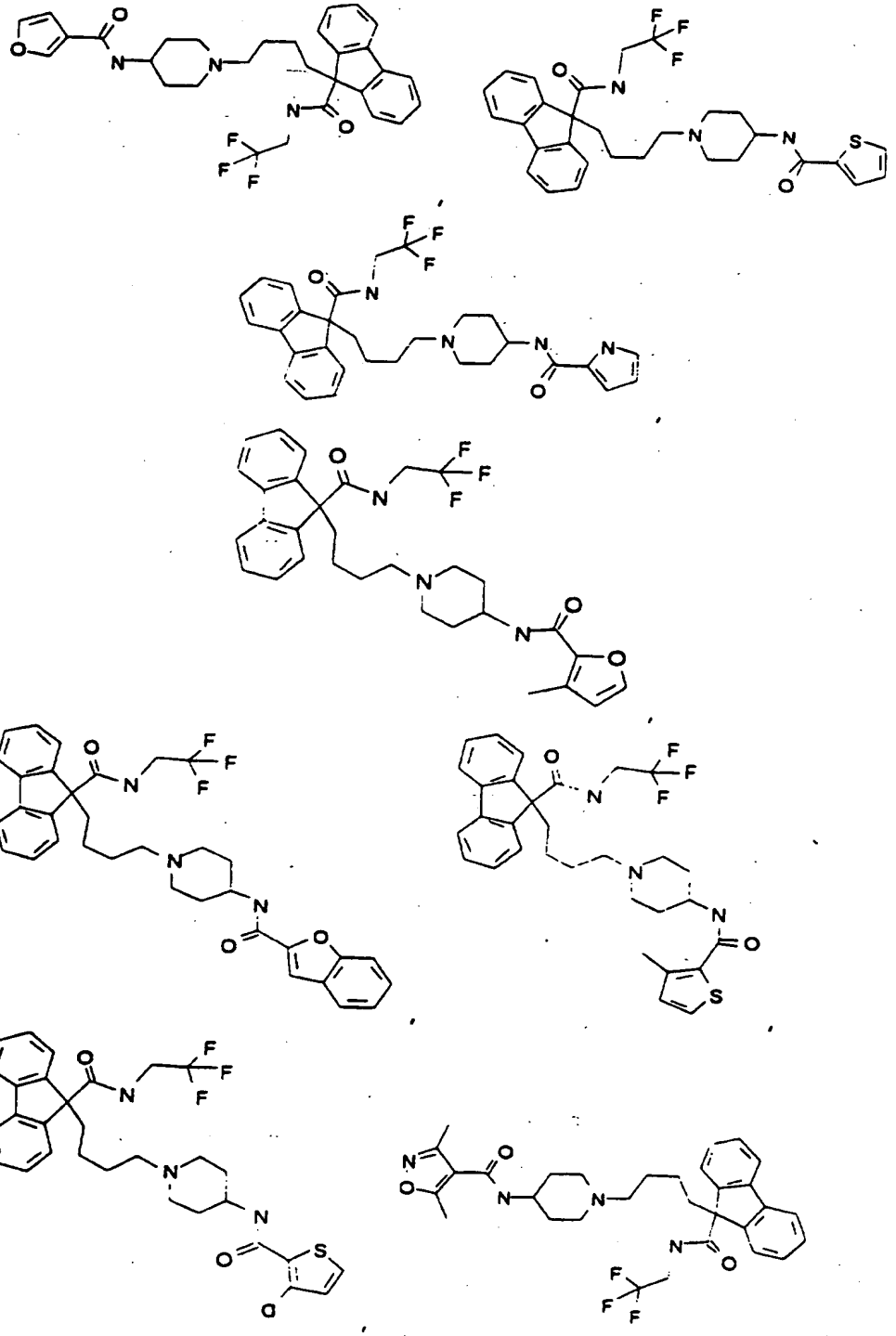

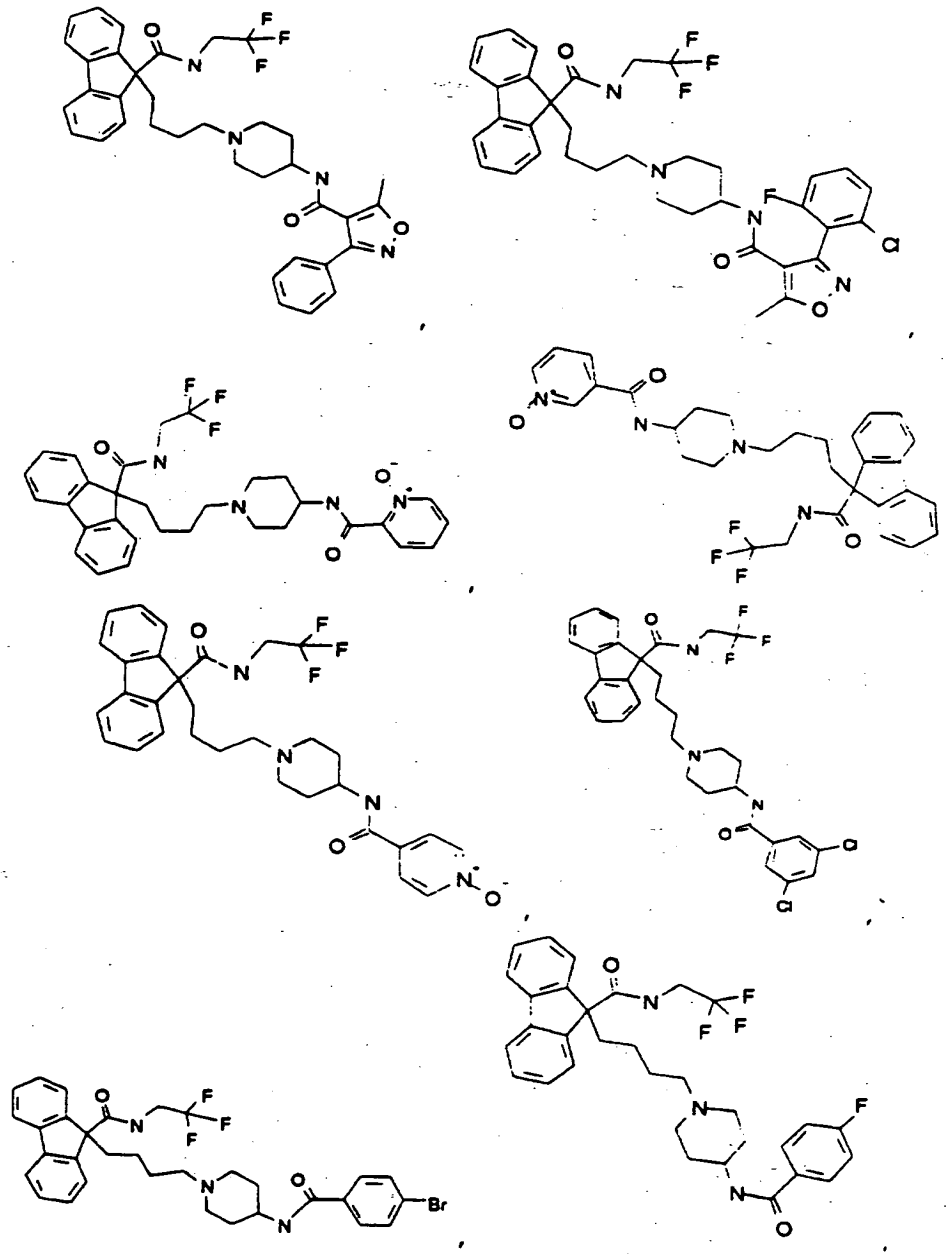

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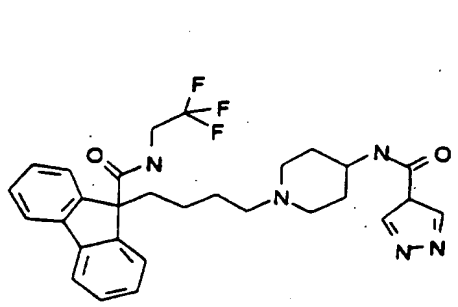

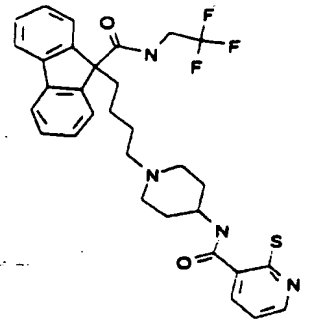

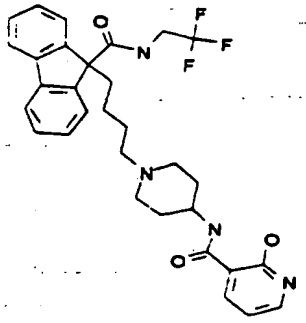

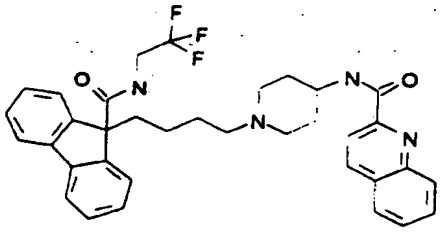

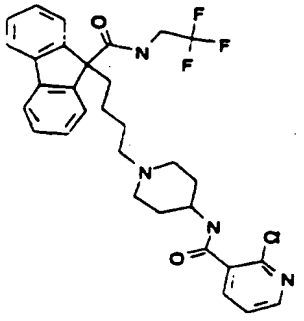

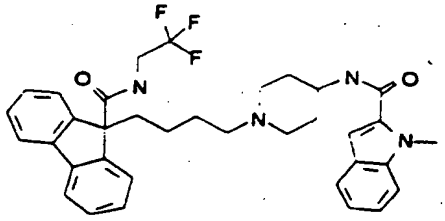

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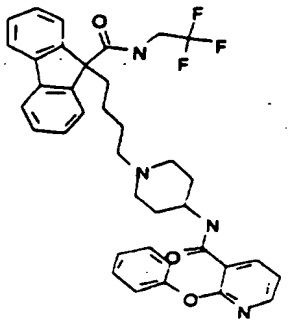

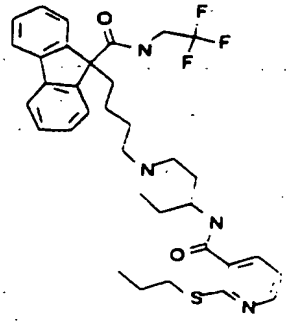

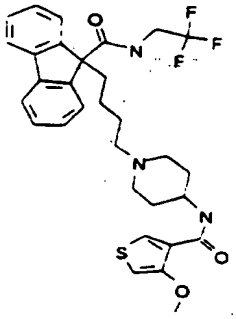

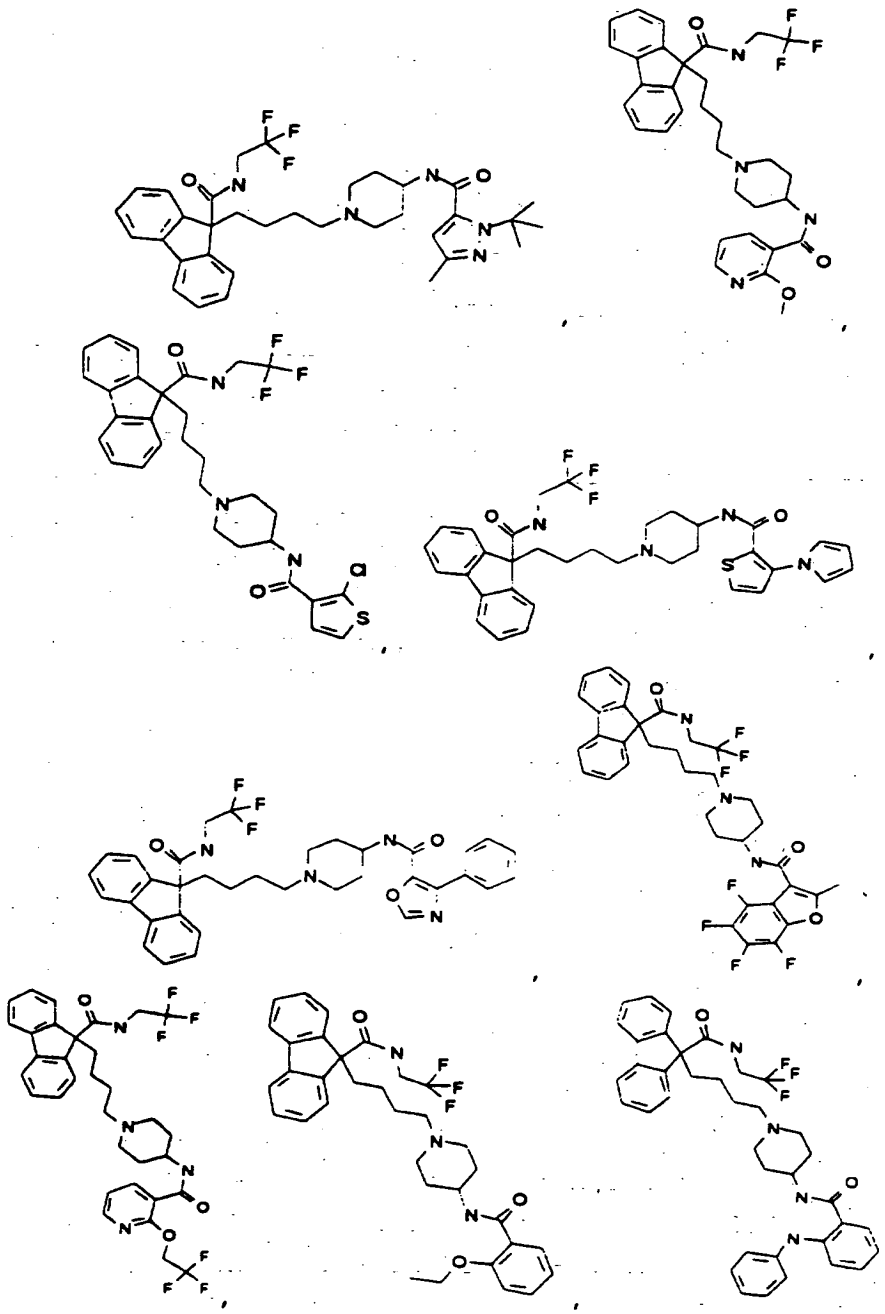

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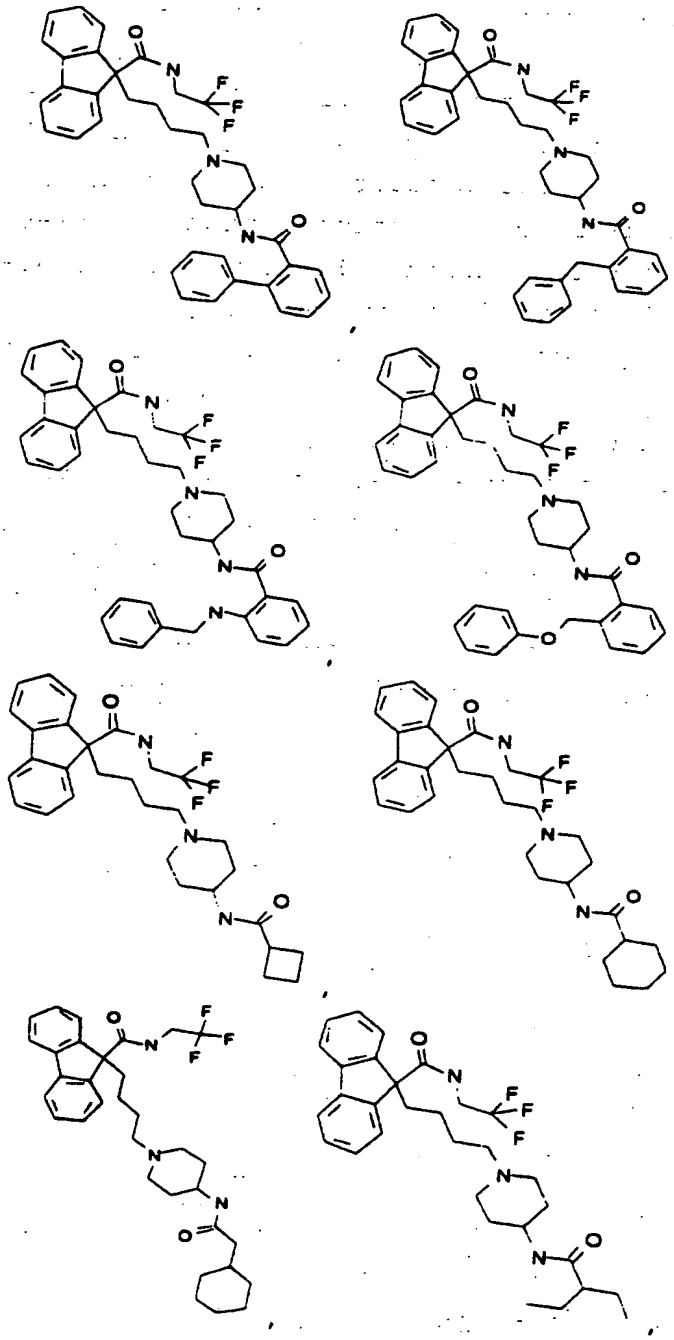

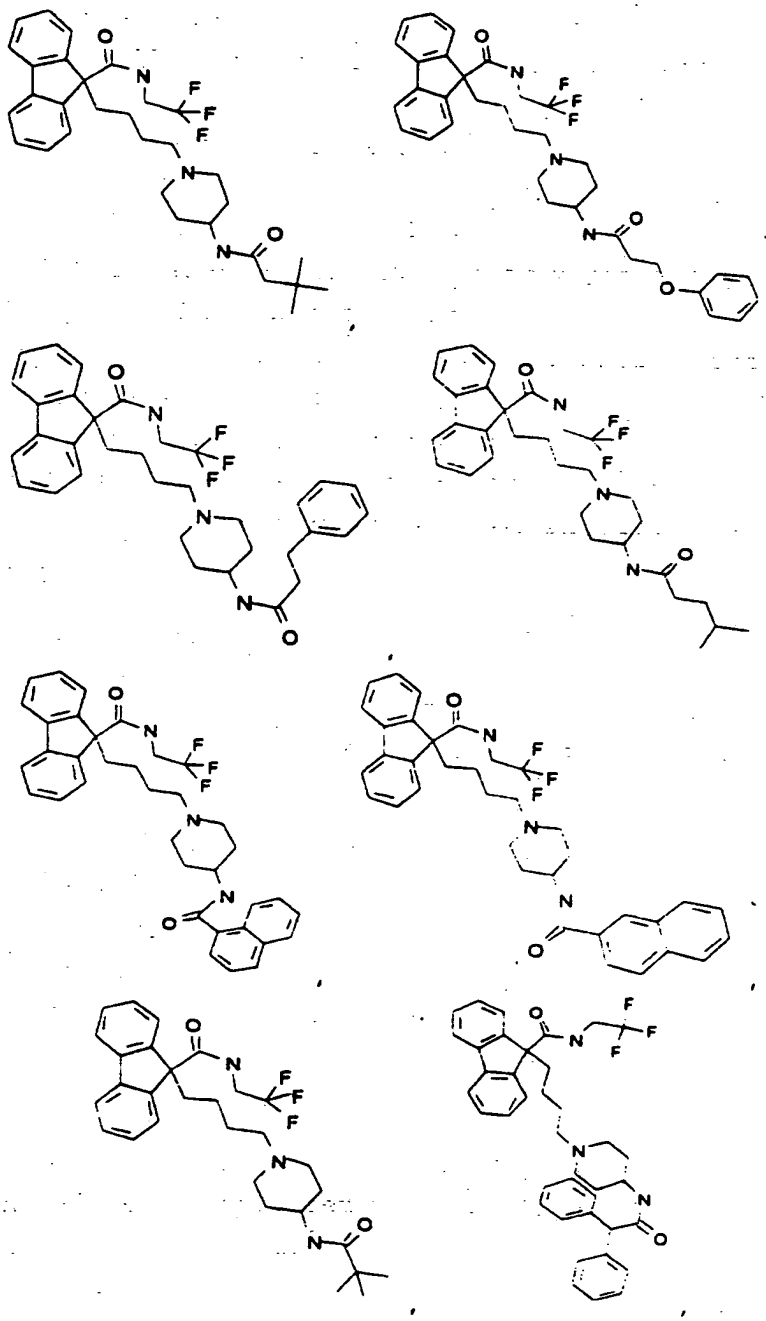

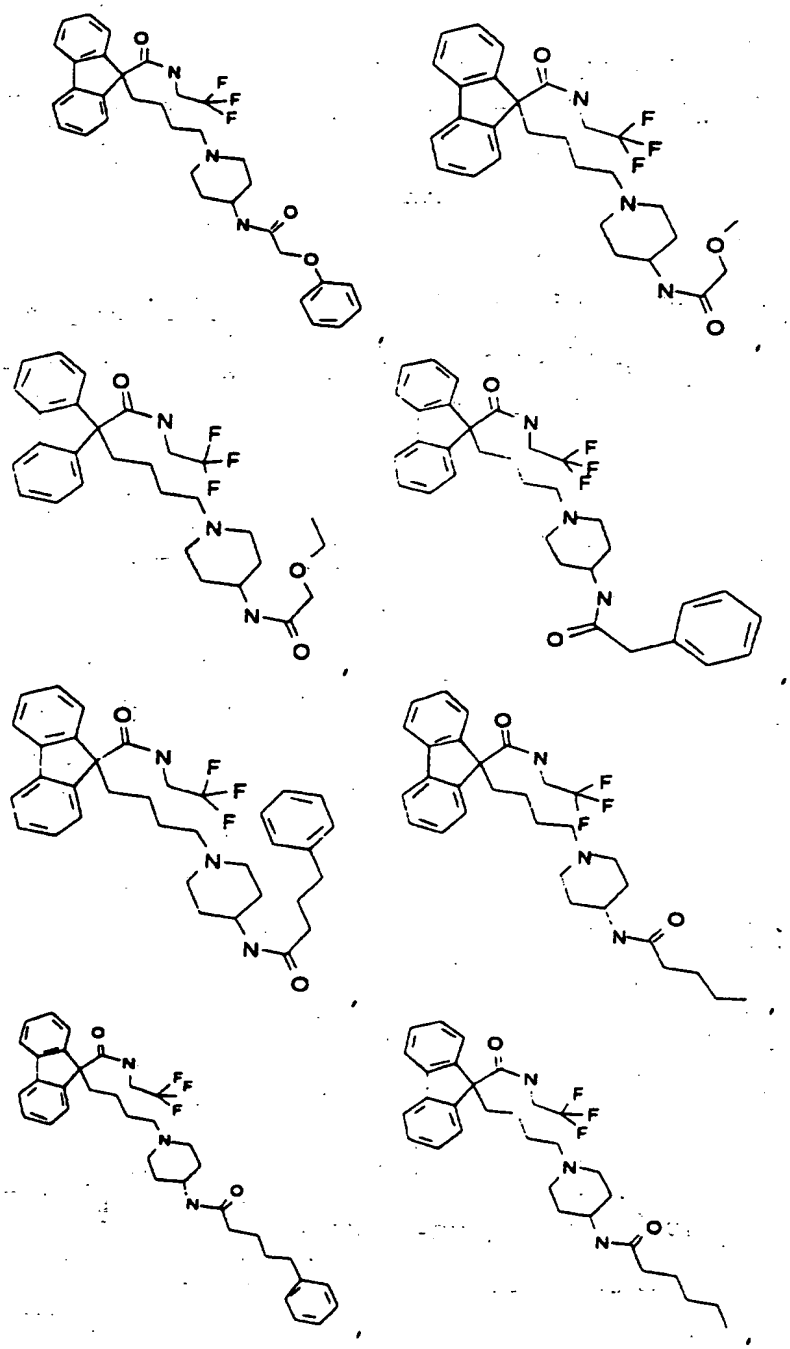

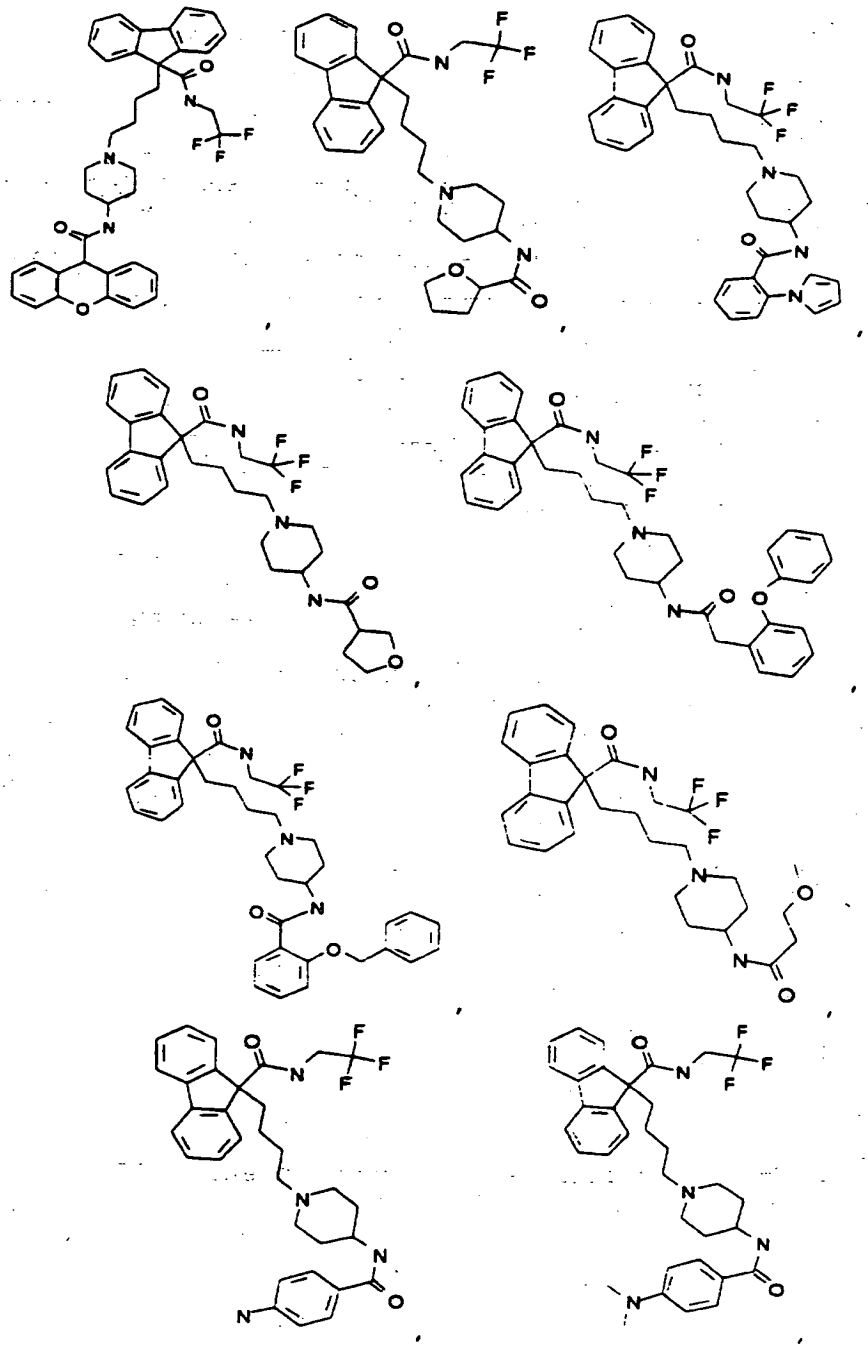

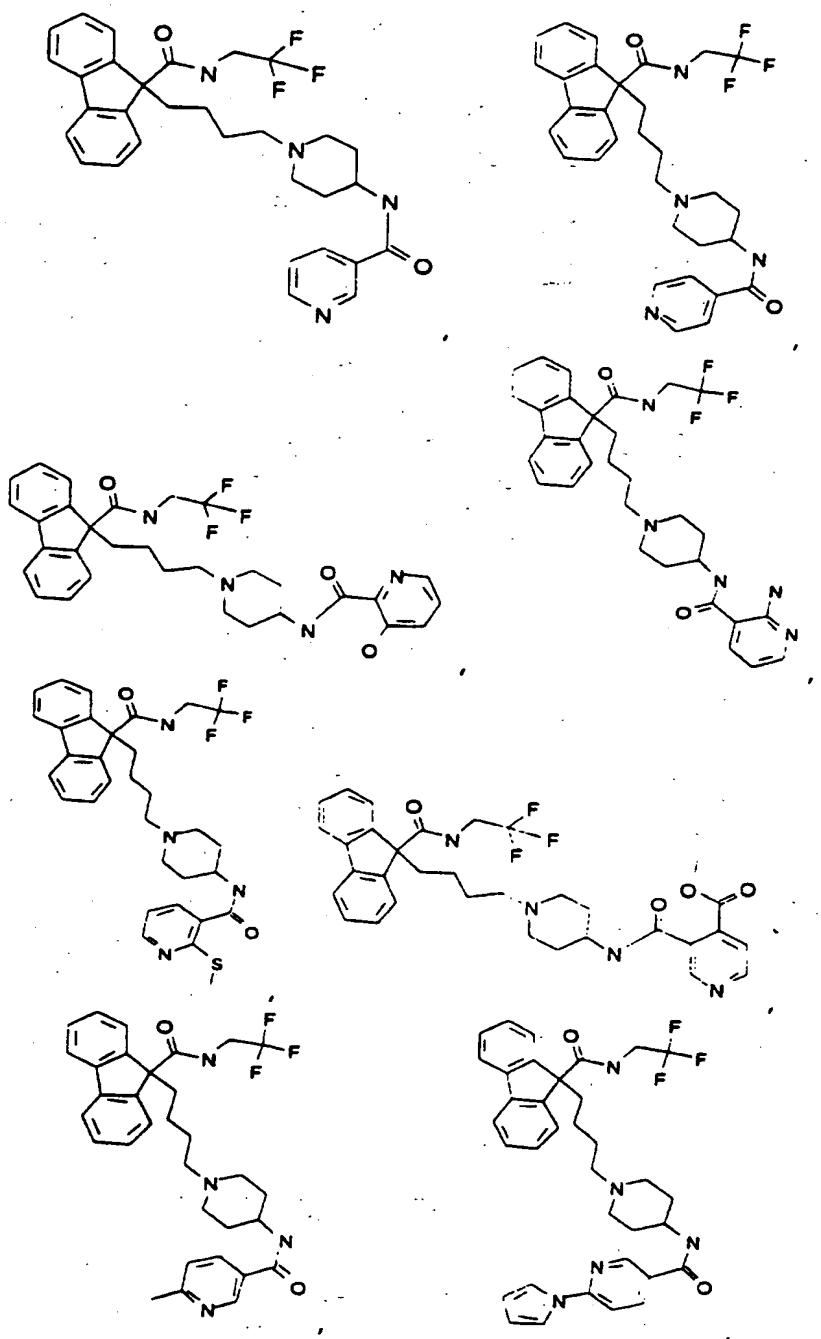

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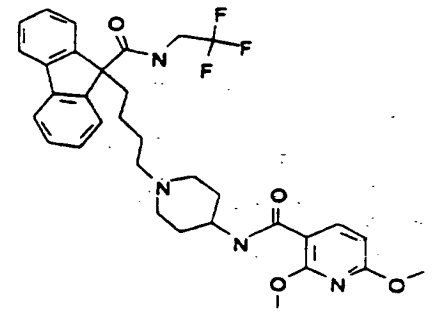

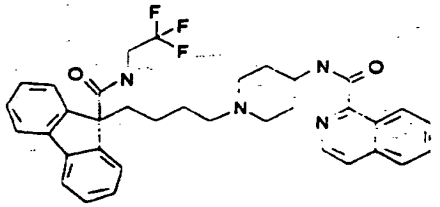

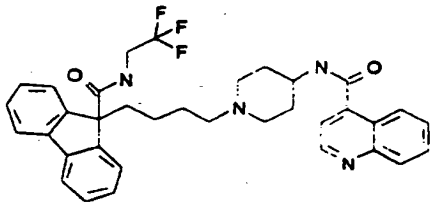

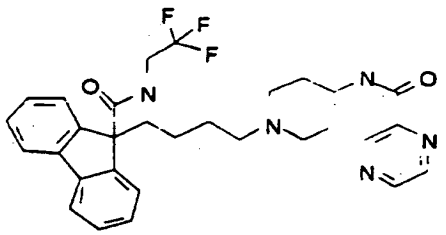

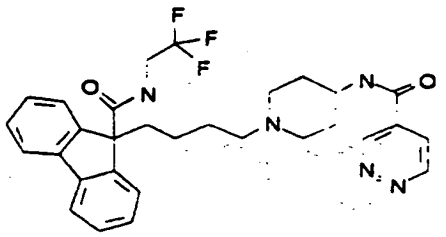

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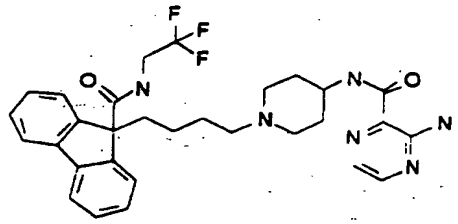

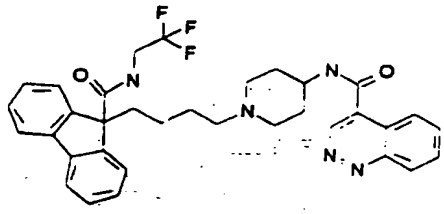

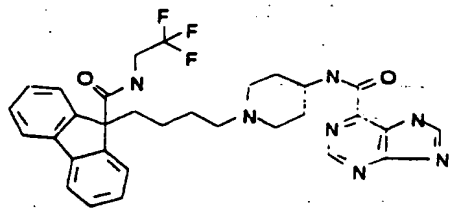

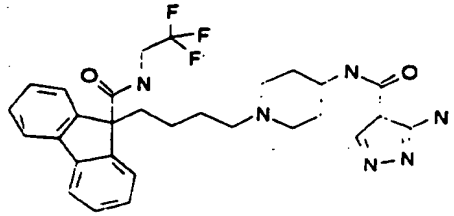

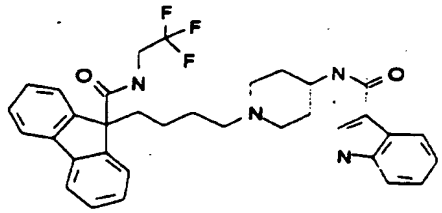

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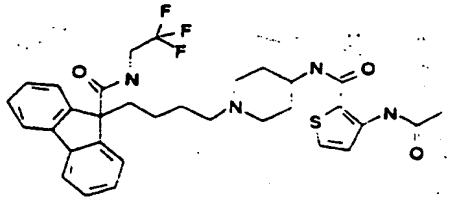

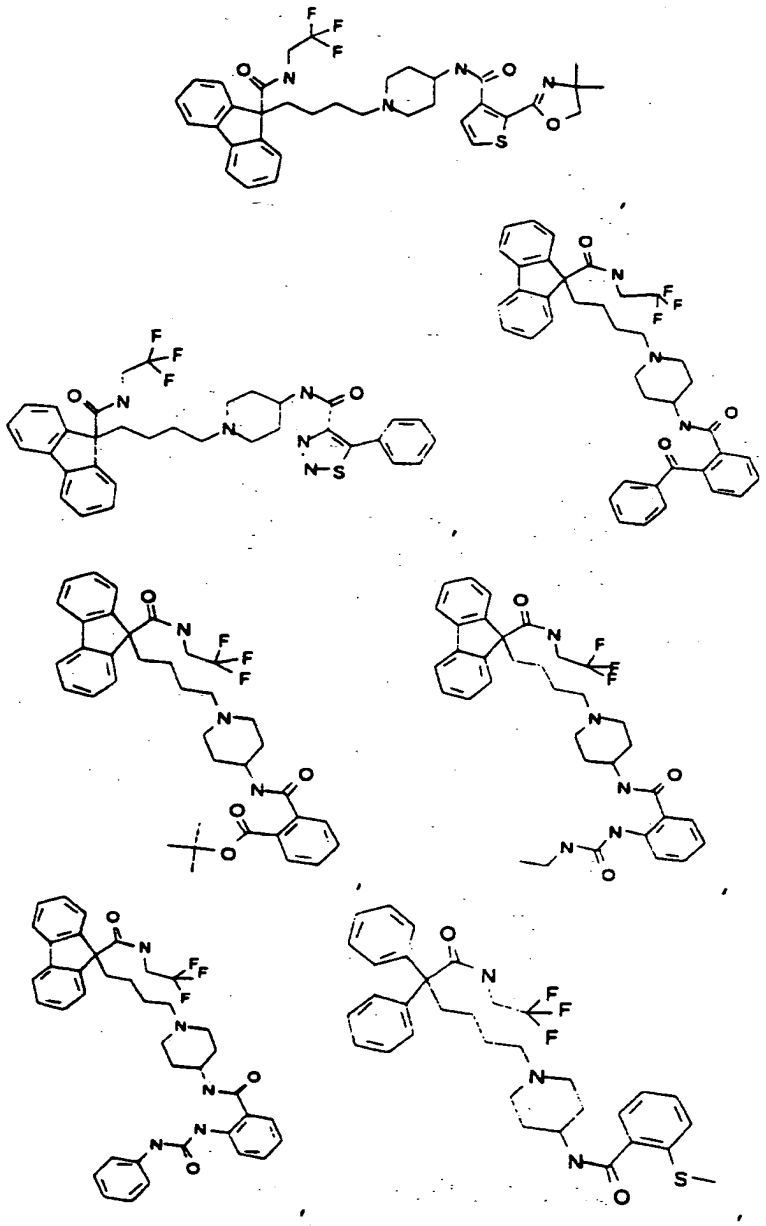

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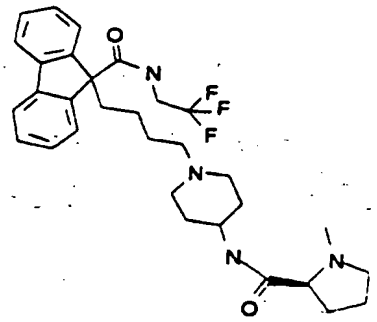
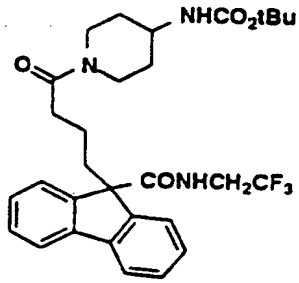


9-[4-[4-[(phenoxycarbonyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[4-[4-[[(phenylamino)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

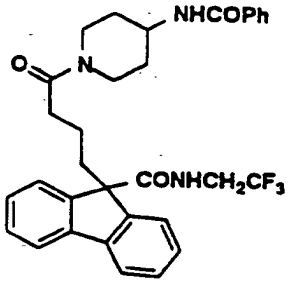
9-[4-[4-[(phenylsulfonyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;



;

cis-9-[4-[4[(2-phenoxybenzoyl)amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide, N-oxide;

9-[4-[4-[(2-phenoxybenzoyl)amino]-1-piperidinyl]-4-oxobutyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;



;

9-[4-[4-[[(1,1-dimethylethoxy)carbonyl]-amino]-1-piperidinyl]pentyl]-N-(2,2,2-trifluoro-ethyl)-9H-fluorene-9-carboxamide;

9-[4-[4-[[(2-phenoxyphenyl)sulfonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[2-[[[4-(benzoylamino)-1-piperidinyl]-carbonyl]amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

[1-[[[2-[9-[[(2,2,2-trifluoroethyl)amino]-carbonyl]-9H-fluoren-9-yl]ethyl]amino]carbonyl]-4-piperidinyl]carbamic acid, 1,1-dimethylethyl ester;

4-[(2-phenoxybenzoyl)amino]-1-piperidine-carboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)-amino]carbonyl]-9H-fluoren-9-yl]ethyl ester;

4-[[(1,1-dimethylethoxy)carbonyl]amino]-1-piperidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoro-ethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl ester;

9-[4-[4-[(2-phenoxybenzoyl)amino]-1-piperidinyl]pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[2-[[[4-[(2-phenoxybenzoyl)amino]-1-piperidinyl]carbonyl]amino]ethyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

4-(benzoylamino)-1-piperidinecarboxylic acid, 2-[9-[[(2,2,2-trifluoroethyl)amino]carbonyl]-9H-fluoren-9-yl]ethyl ester;

9-[4-[4-(benzoylamino)-1-piperidinyl]pentyl]-N-(2,2,2-trifluoroethyl)-9H-fluorene-9-carboxamide;

9-[4-[4-[[(1,1-dimethylethoxy)carbonyl]-amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoro-ethyl)-9H-thioxanthene-9-carboxamide;

9-[4-[4-(benzoylamino)-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide;

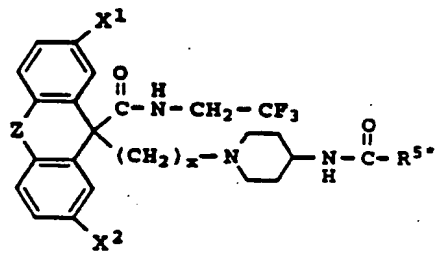
9-[4-[4-[[(2-phenoxyphenyl)carbonyl]amino]-1-piperidinyl]butyl]-N-(2,2,2-trifluoroethyl)-9H-thioxanthene-9-carboxamide;

and a pharmaceutically acceptable salt of any of the above and an N-oxide of any of the above.

12. A method for preventing, inhibiting or treating atherosclerosis, pancreatitis or obesity in a mammalian species, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1 or 14.

13. A method of lowering serum lipid levels, cholesterol and/or triglycerides, or inhibiting and/or treating hyperlipemia, hyperlipidemia, hyperlipoproteinemia, hypercholesterolemia and/or hypertriglyceridemia, which comprises administering to a patient in need of treatment a therapeutically effective amount of a compound as defined in Claim 1 or 14.

14. A compound having the structure



including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof, wherein Z is a bond, O or S;

X^1 and X^2 are independently selected from H or halo;

x is an integer from 2 to 6;

R^{5*} is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each R^{5*} group being optionally substituted with 1, 2, 3 or 4 substituents which may be the same or different.

15. The compound as defined in Claim 14 wherein Z is a bond, each of X^1 and X^2 is H.

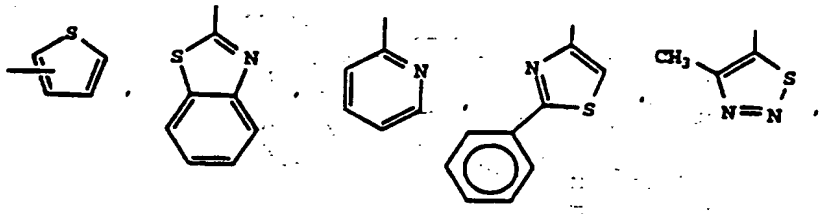
16. The compound as defined in Claim 14 which is a piperidine N-oxide.

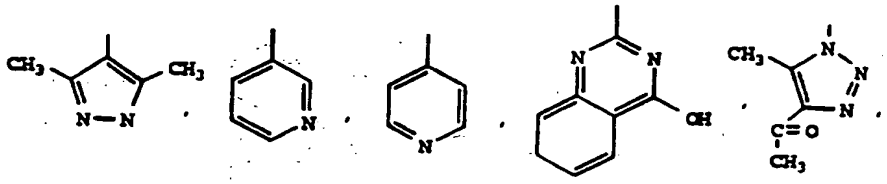
17. The compound as defined in Claim 14 wherein the substituent on R^{5*} is adjacent to the carbon attached to the $\overset{O}{\overset{\|}{C}}$ group.

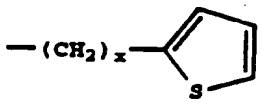
18. The compound as defined in Claim 14 wherein R^{5*} is substituted with 1, 2, 3 or 4 substituents which may be the same or different and are halogen, monocyclic heteroaryl, bicyclic heteroaryl, heteroarylalkyl, cycloheteroalkyl, alkyl, alkoxy, cycloalkyl, aryl, aryloxy, substituted aryl, arylalkyloxy, heteroaryloxy, amino, alkylamino, alkyl(aryl)amino, heteroarylamino, arylamino, alkylthio, arylthio, arylthioalkyl, heteroarylthio, arylsulfinyl or acyl.

19. The compound as defined in Claim 18 wherein R^{5*} is substituted with 1, 2, 3 or 4 of one or more of the following

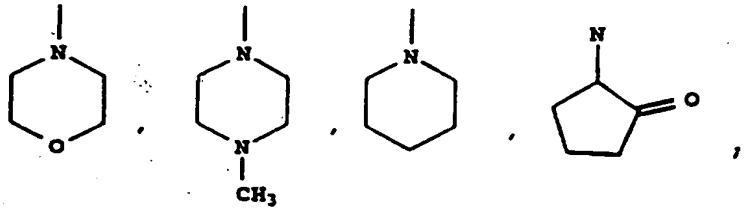
I, Cl, F, CF_3

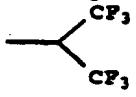




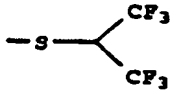


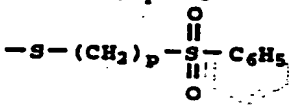
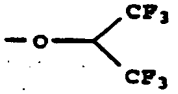
where x is 1 to 5

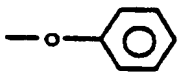
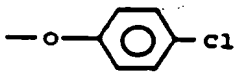


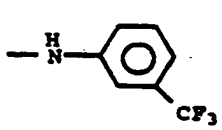
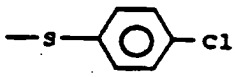
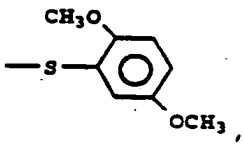
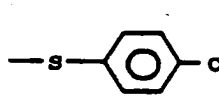
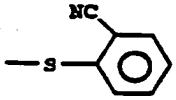
alkyl, phenyl, phenyl substituted with halo, alkyl, CF_3O, alkoxy,  , CF_3, or phenyl;

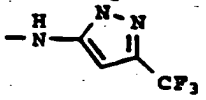
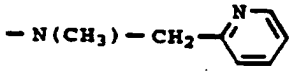
$-\overset{H}{N}-(CH_2)_pCF_3-$ where p is 1 to 5, $-N(CH_3)C_6H_5$;

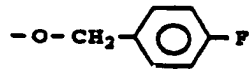
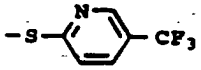
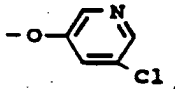
$-S-(CH_2)_pCF_3$ where p is 1 to 5,  , -S-alkyl,

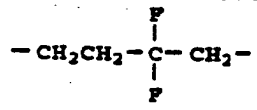
 , $-O-(CH_2)_p-CF_3$,  , OCH_3;

cyclohexyl,  ,  ;

amino,      ;

alkanoyl, alkoxycarbonyl, aroyl, heteroarylaminocarbonyl, arylalkyloxycarbonyl,   ;

$-CH_2-S-C_6H_5$,    ,

20. The compound as defined in Claim 19 wherein $(CH_2)_x$ is $(CH_2)_4$ or  ;

Z is a bond;

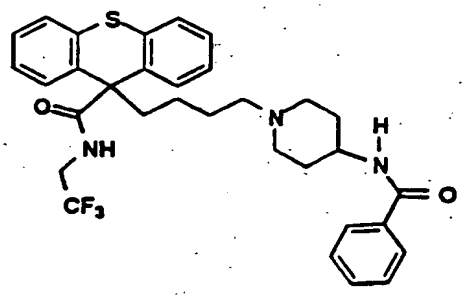
X^1 and X^2 are H;

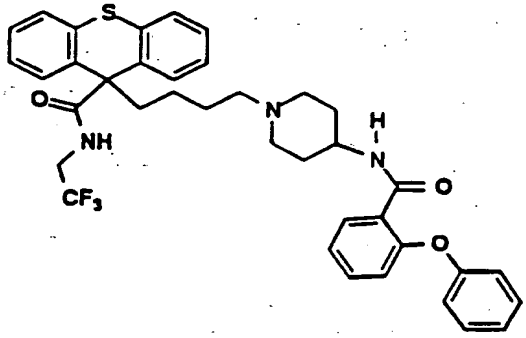
R^{5*} is aryl, which is substituted with trifluoromethylphenyl, heteroaryl, halo and/or aryl or

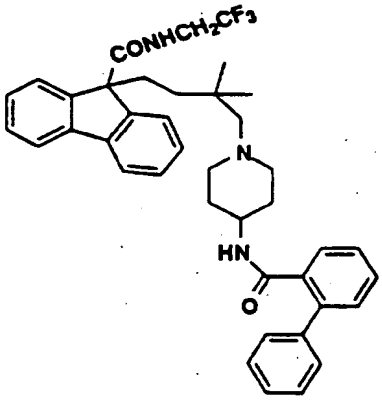
R^{5*} is heteroaryl

wherein the R^{5*} includes a substituent attached to a carbon adjacent to the carbon linked to .

21. The compound as defined in Claim 14 which is







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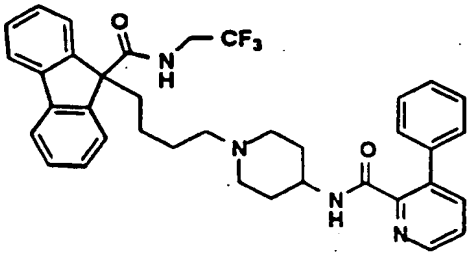
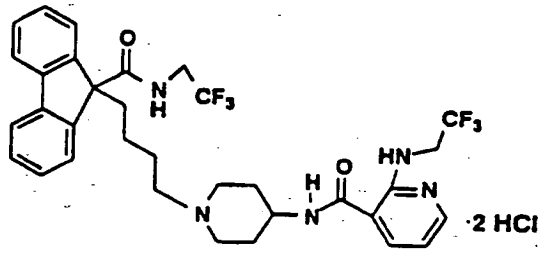
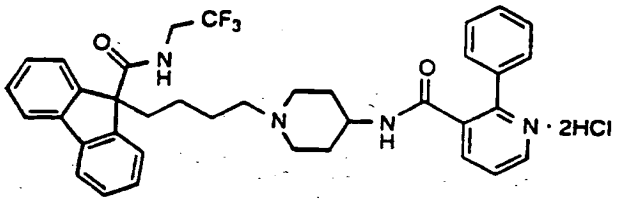
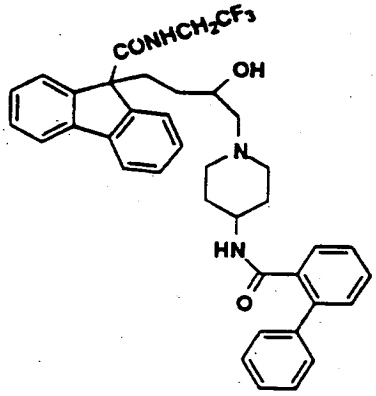
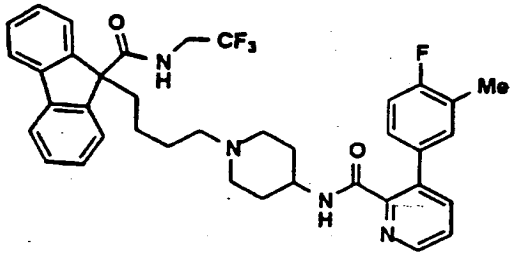


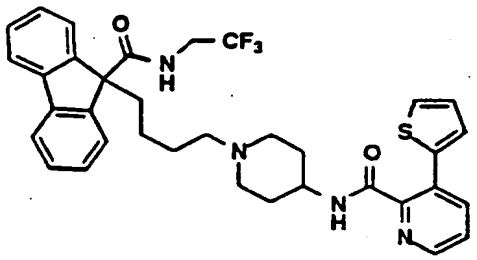

O
N
H
CF3
CF3
HN
H
O
N
N
N
·2 HCl

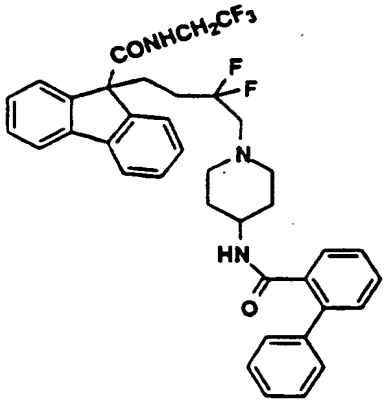

CF3
O
N
H
N
N
H
O
N · 2HCl

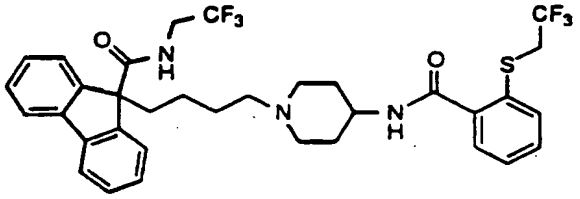

CONHCH2CF3
OH
N
HN
O

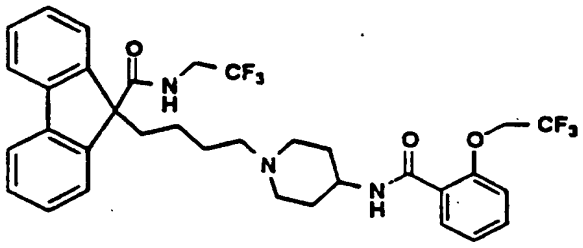
5

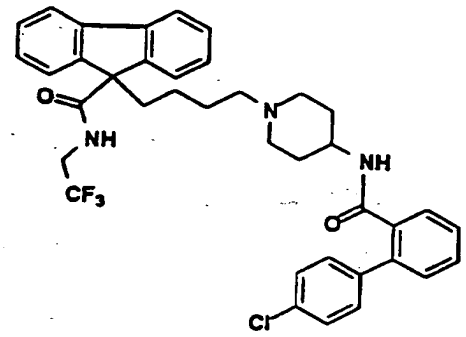

O
N
H
CF3
F
Me
N
O
N
H
N

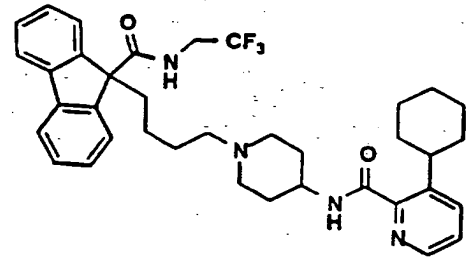


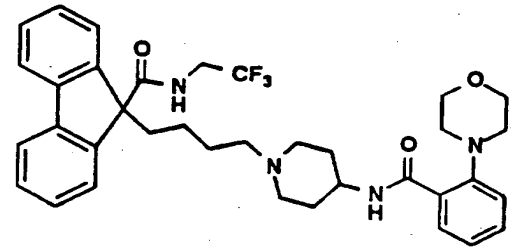












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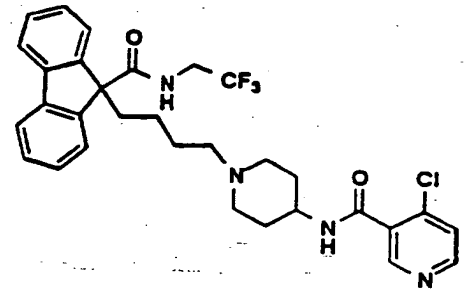

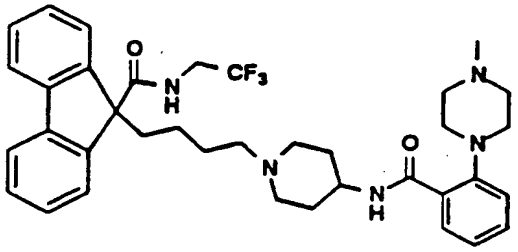

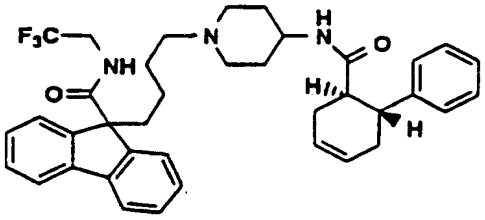

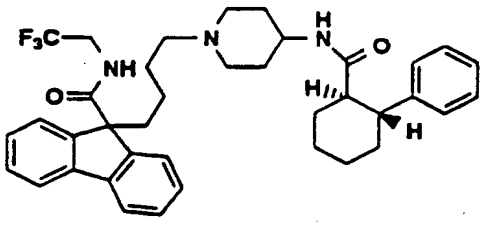

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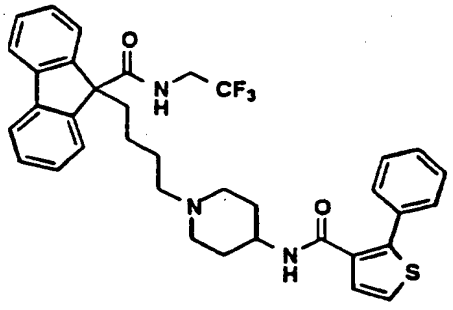

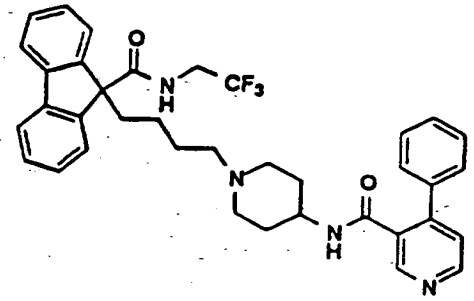

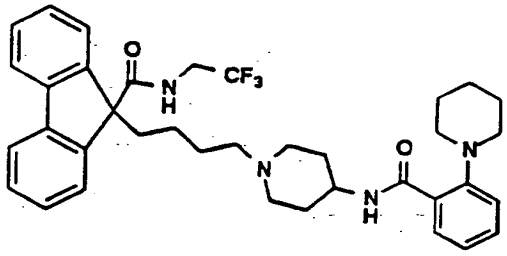

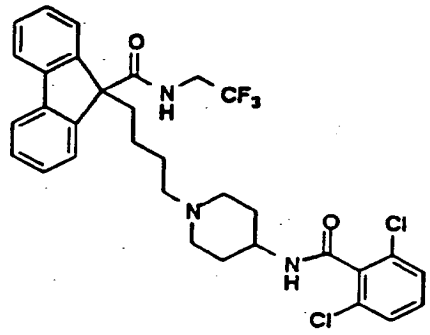

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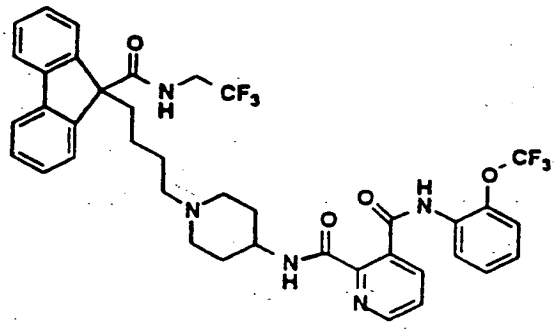

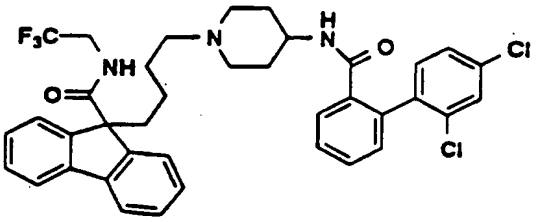

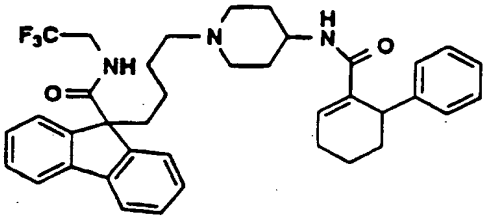

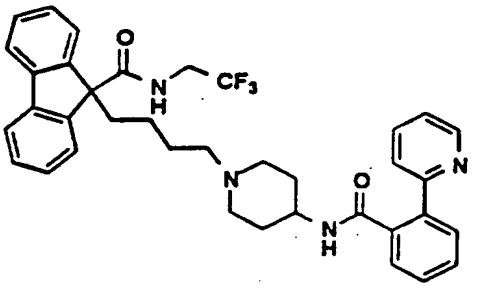

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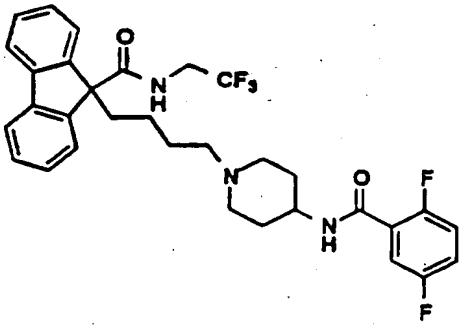

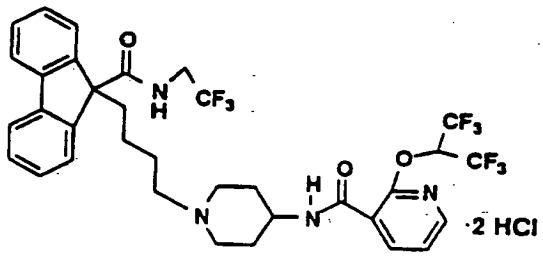

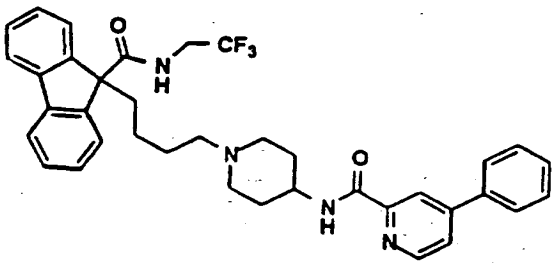

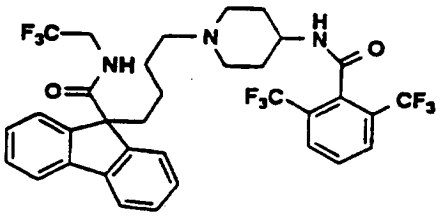

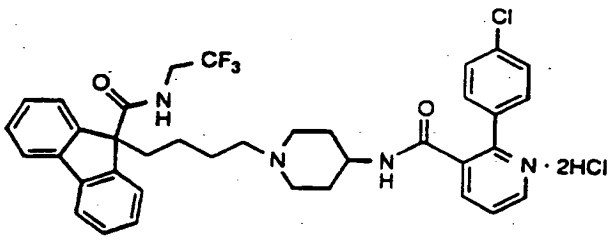

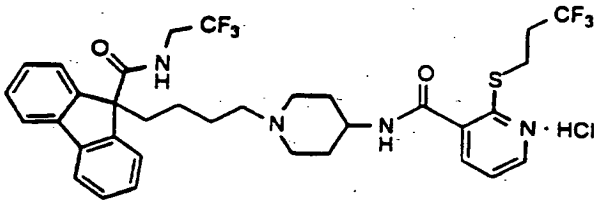

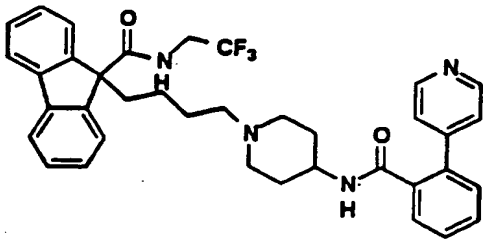

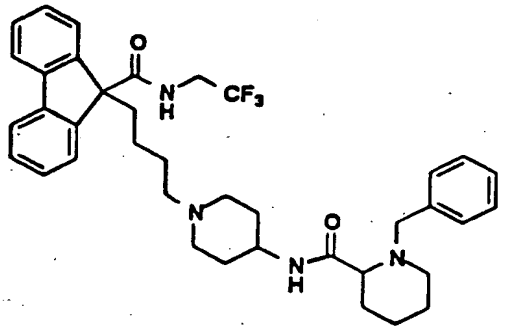

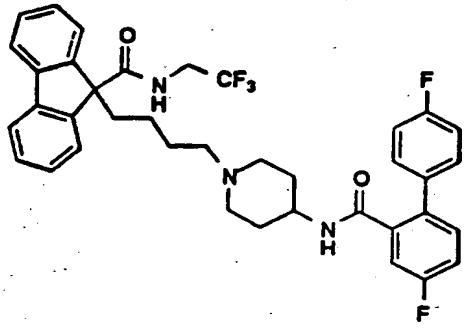

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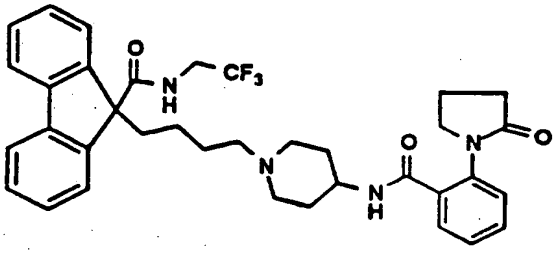

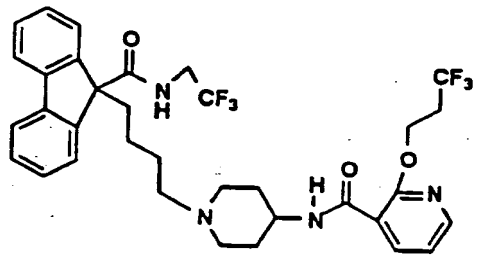

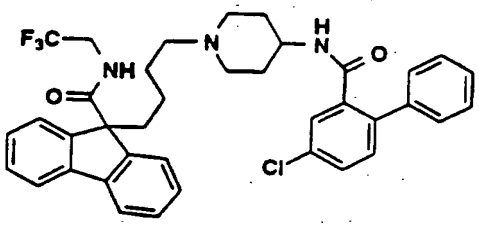

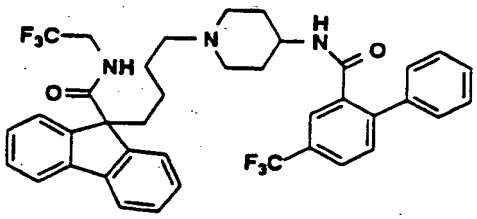

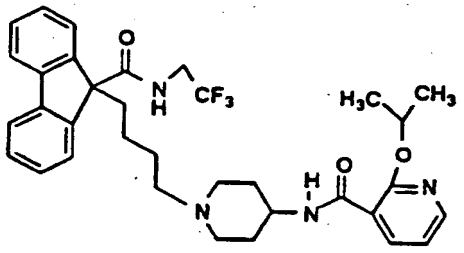

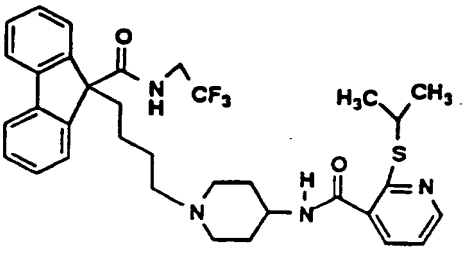

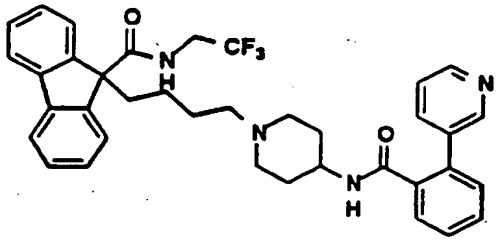

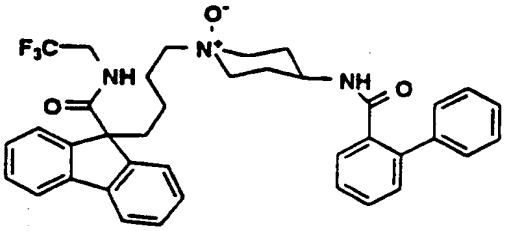

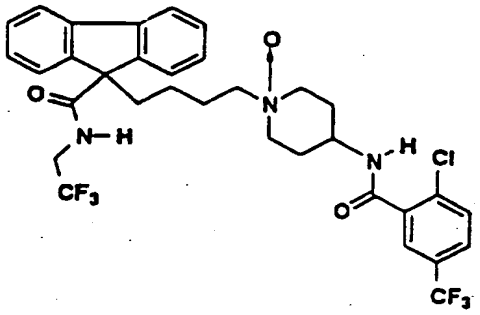

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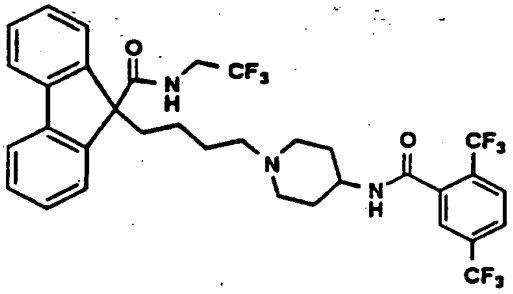

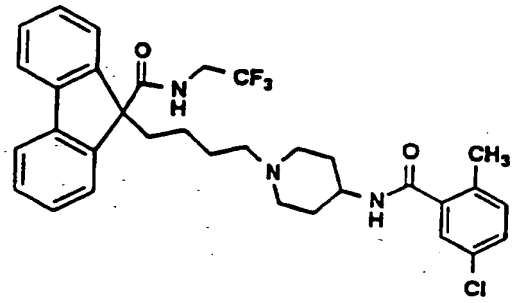

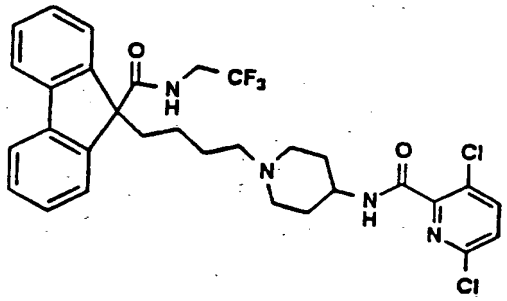

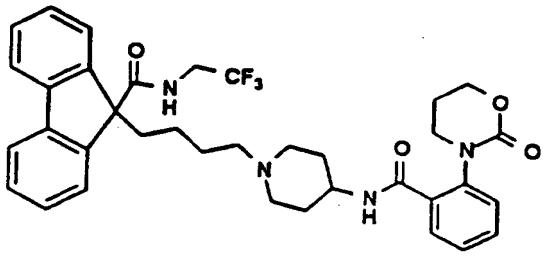

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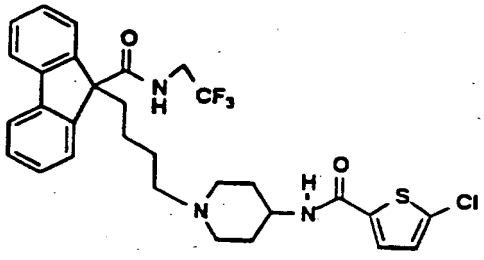

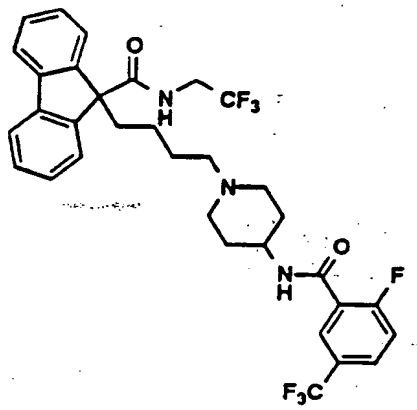

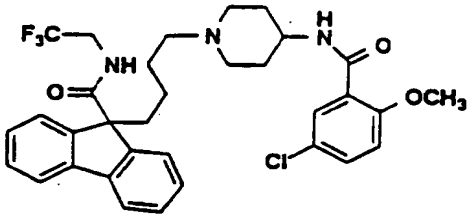

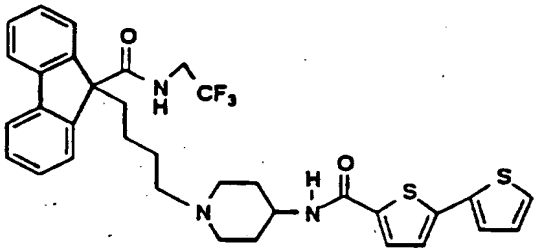

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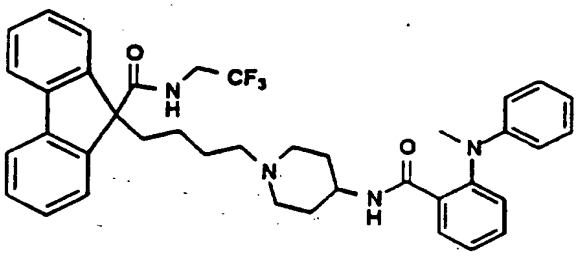

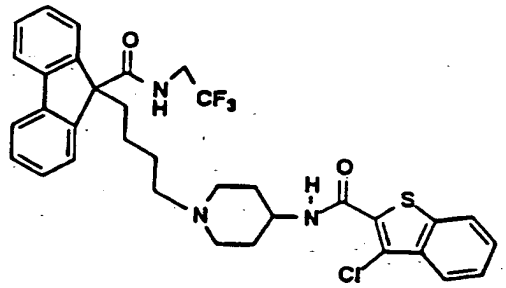

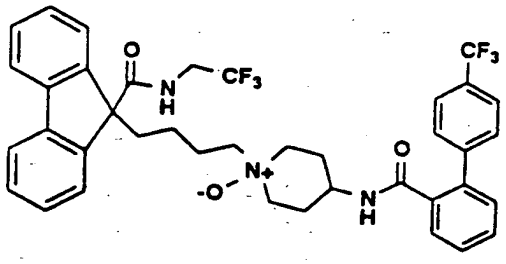

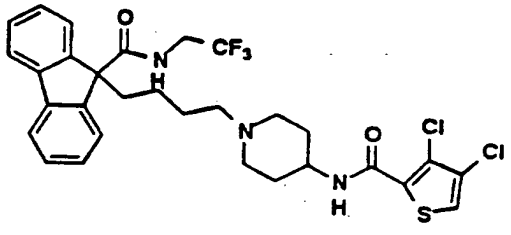

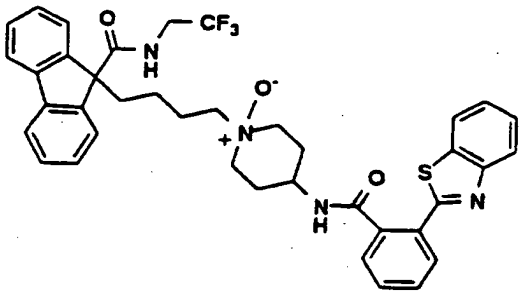

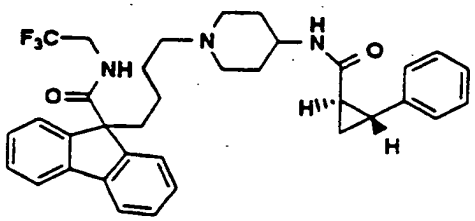

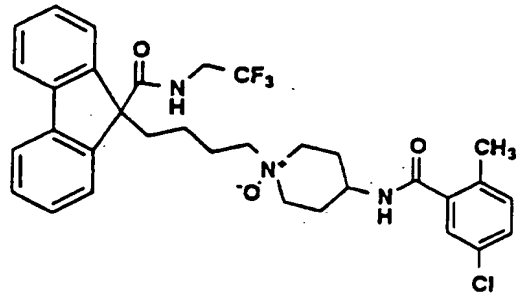

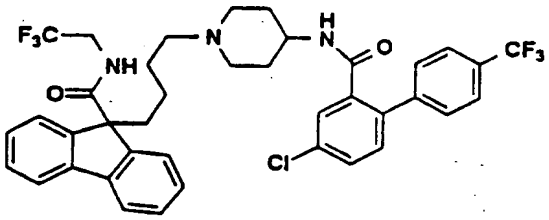

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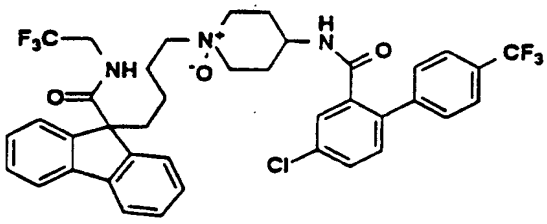

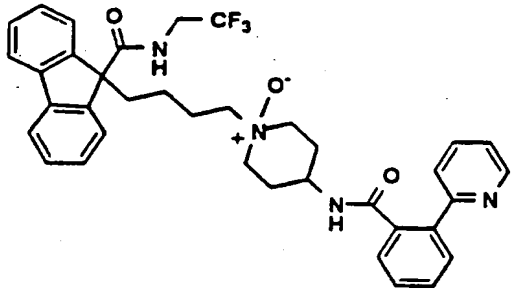

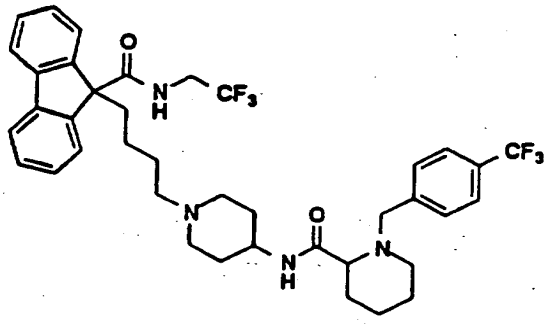

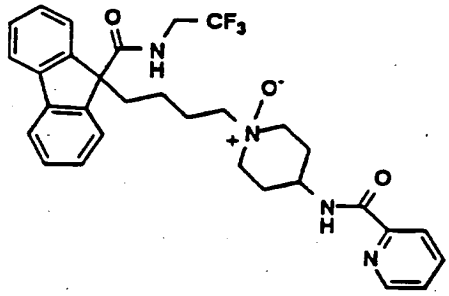

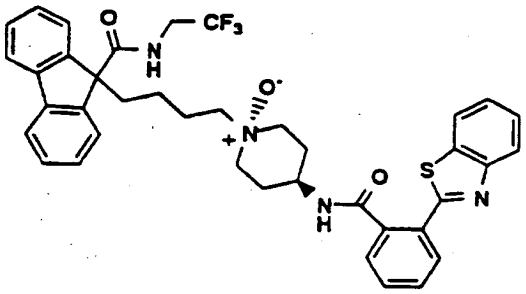

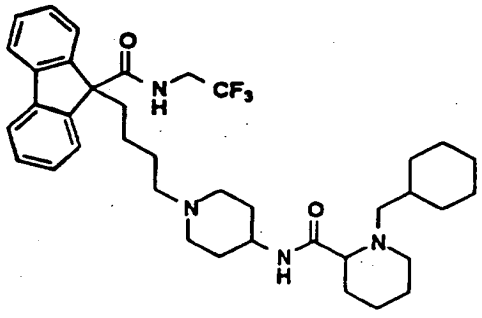

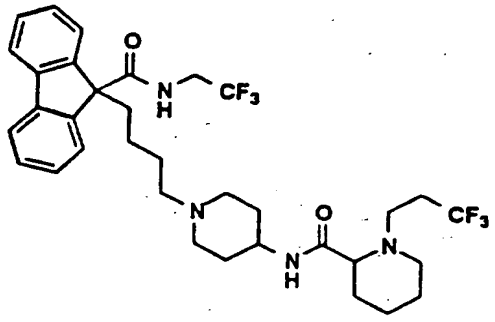

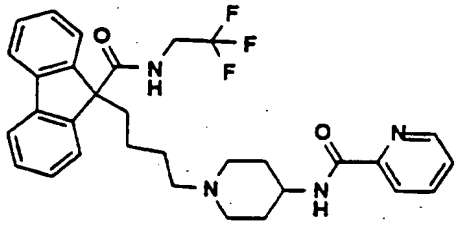

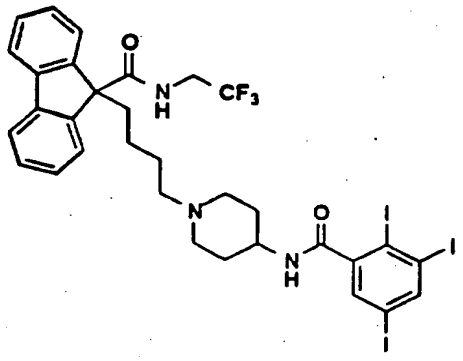

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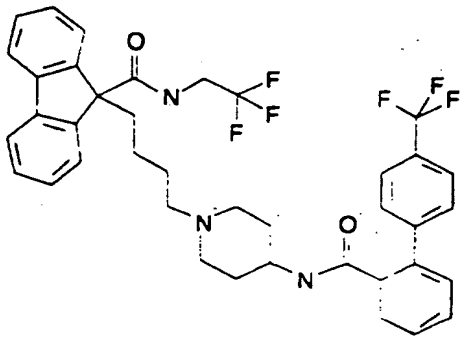

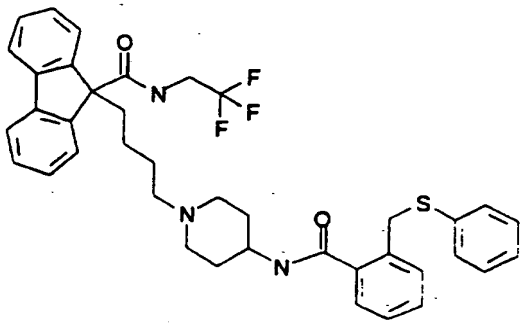

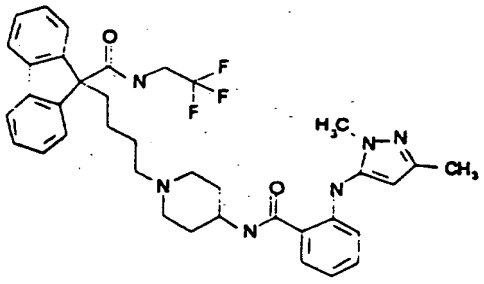

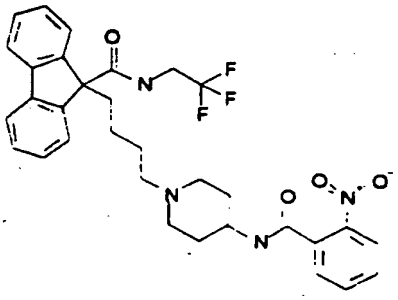

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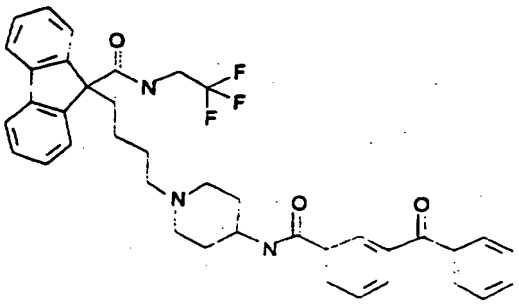

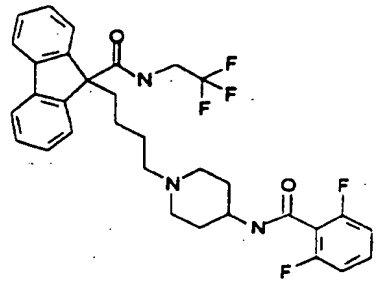

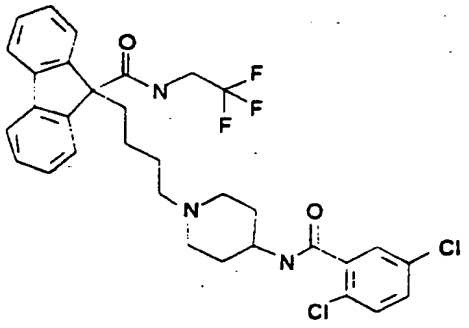

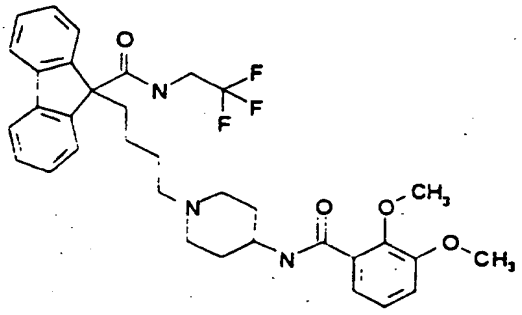

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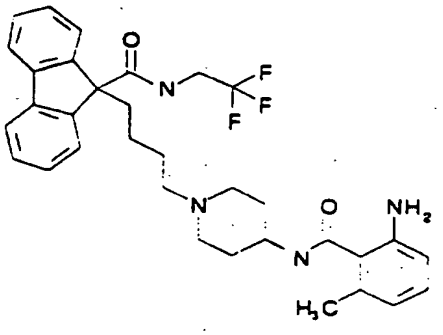

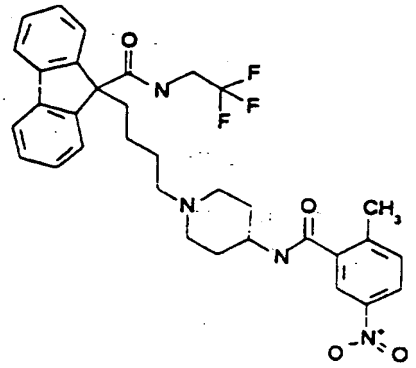

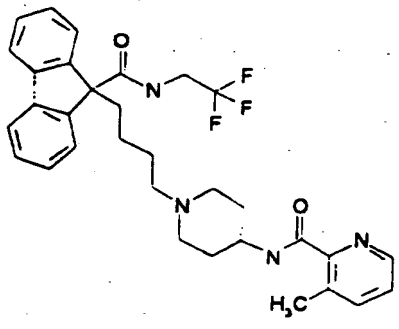

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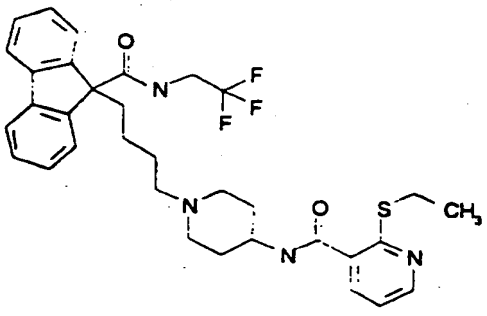

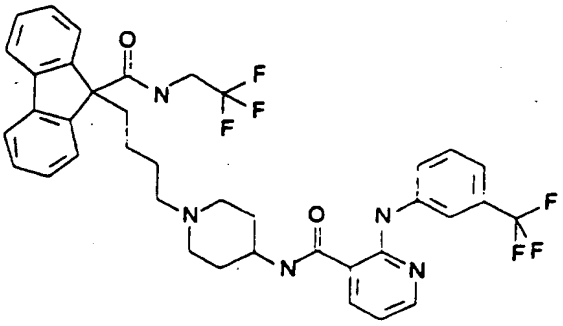

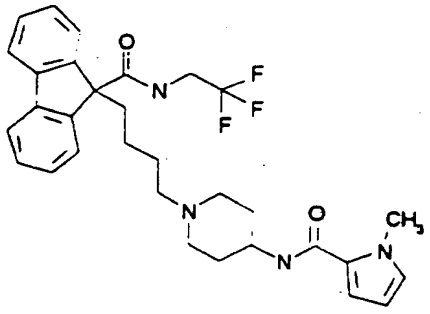

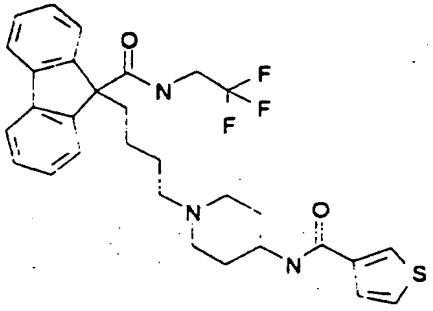

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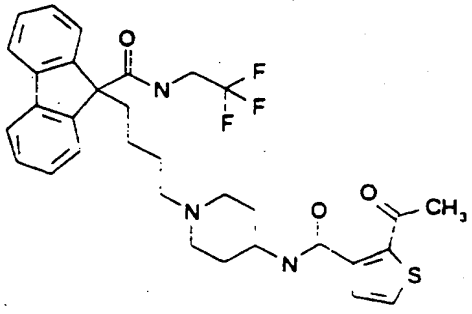

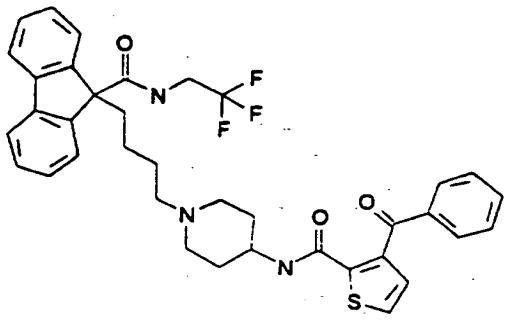

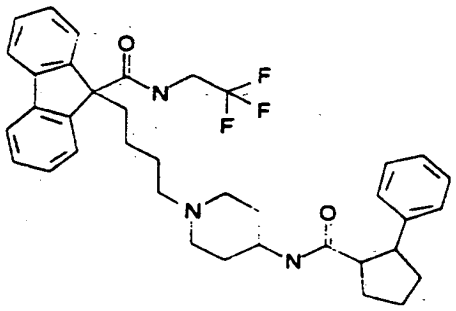

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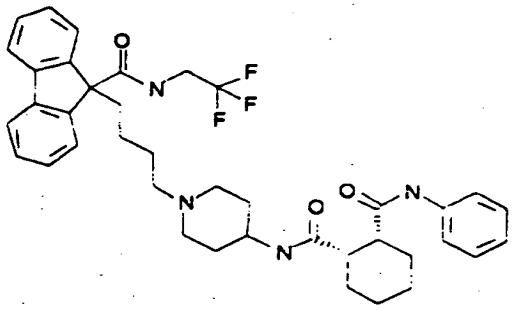

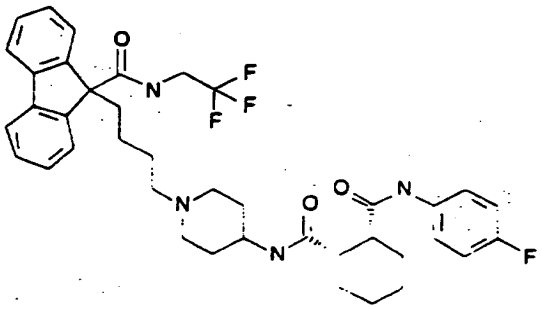

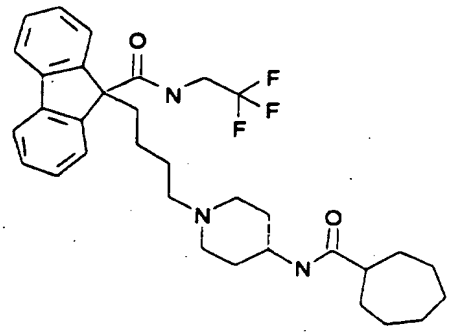

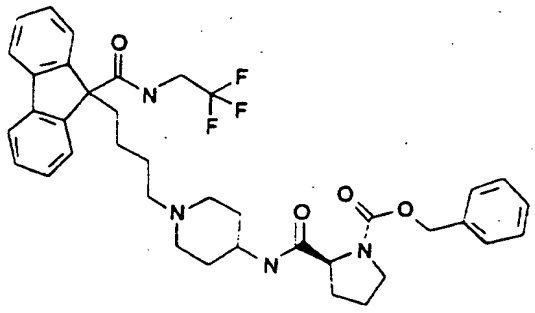

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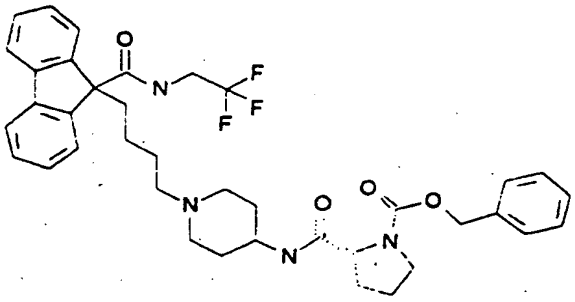

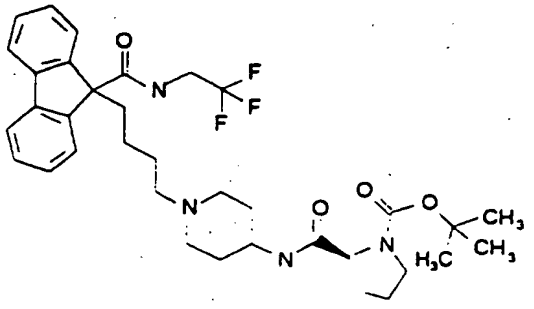

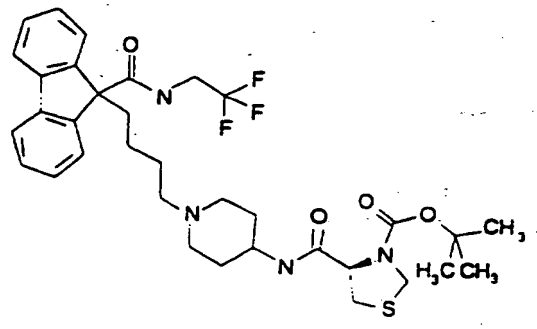

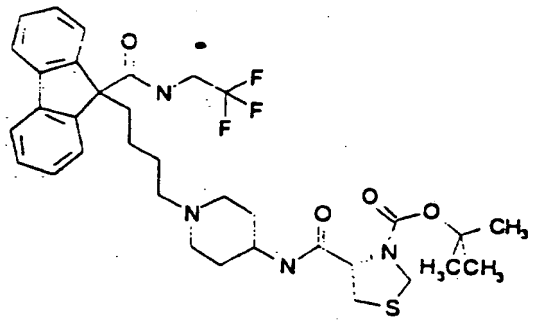

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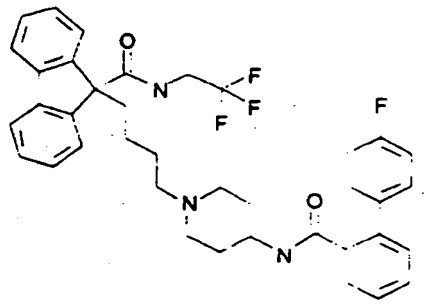

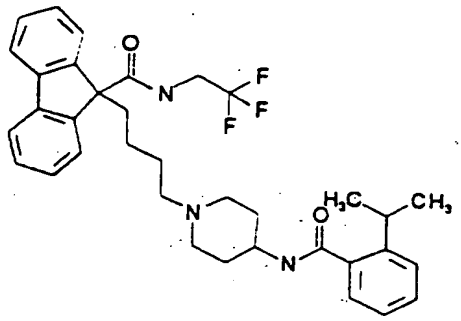

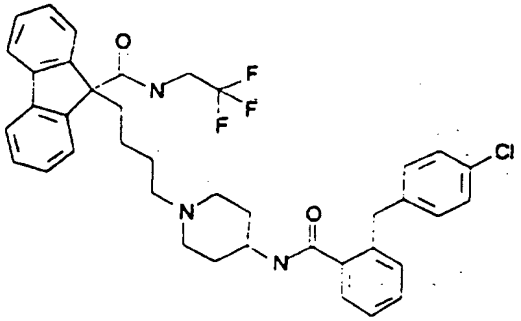

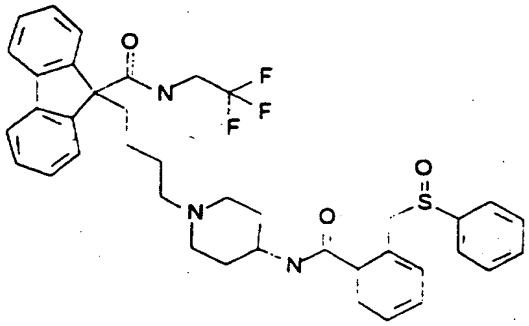

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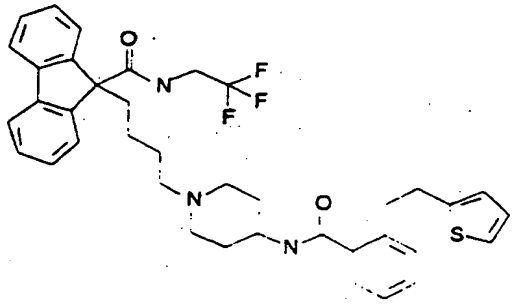

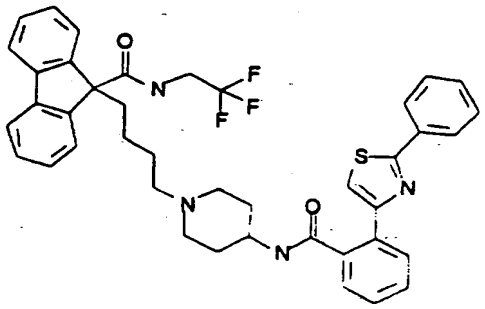

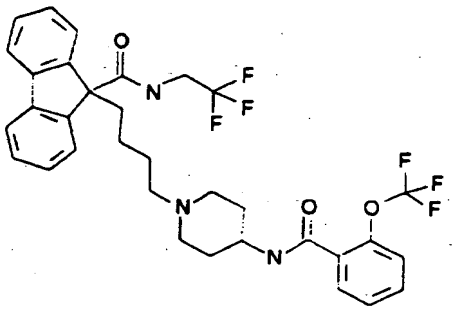

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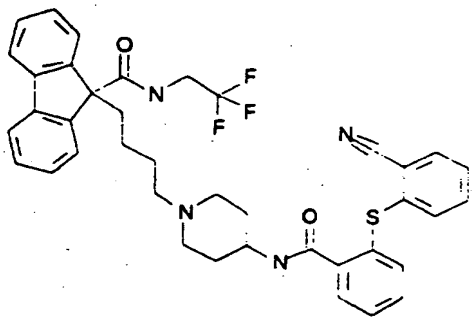

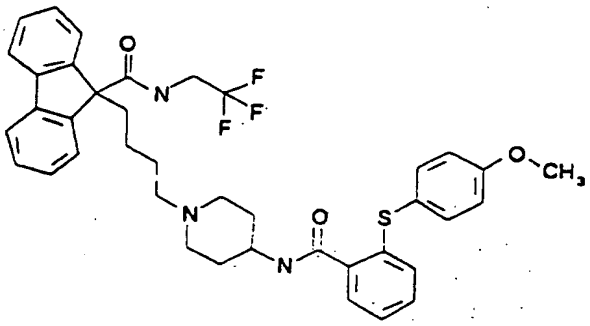

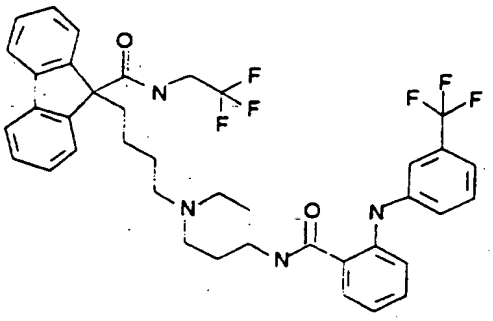

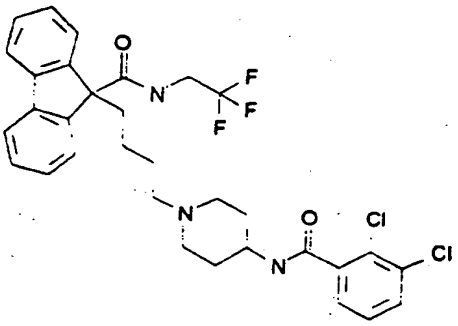

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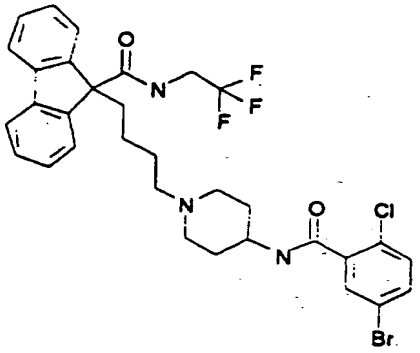

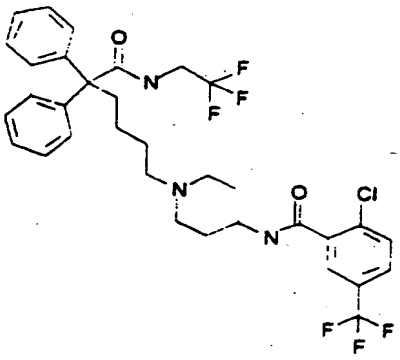

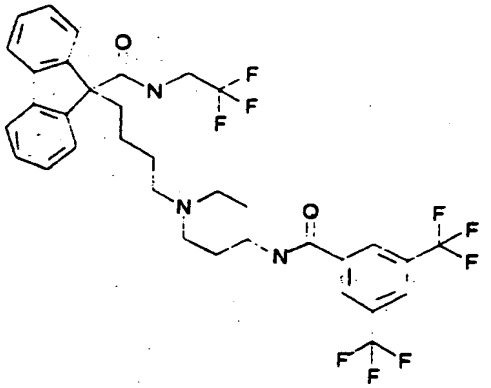

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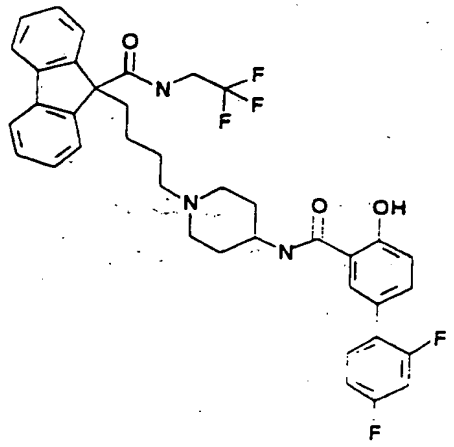

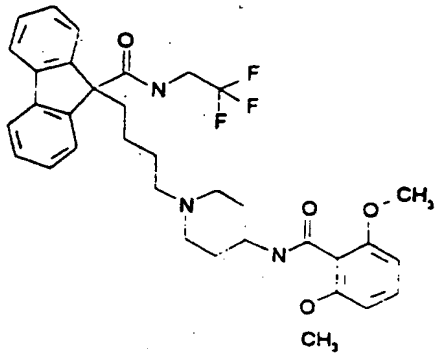

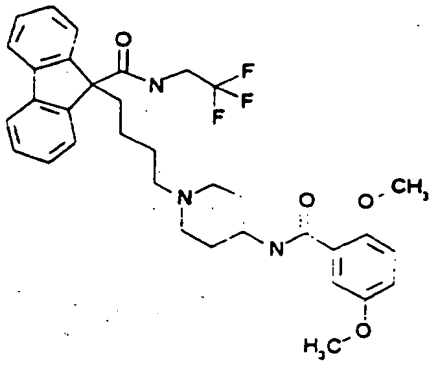

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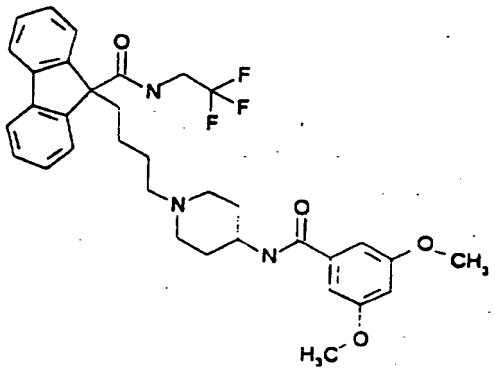

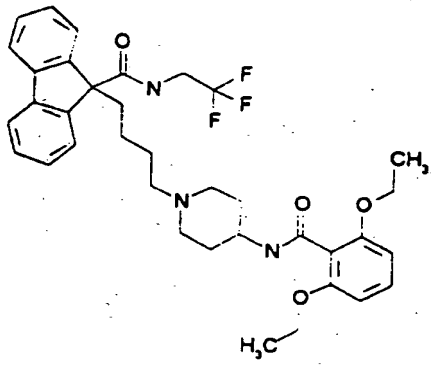

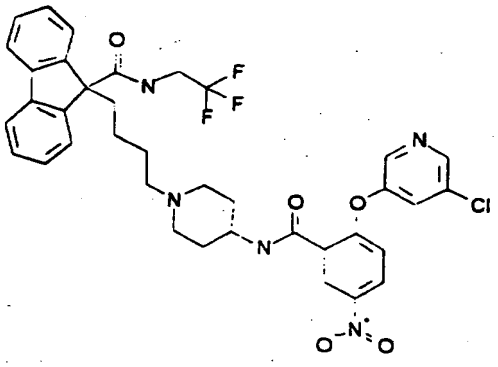

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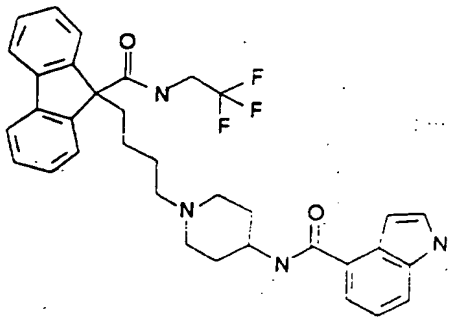

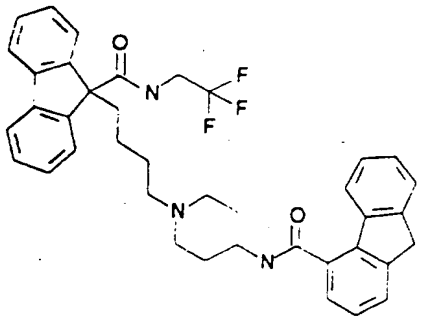

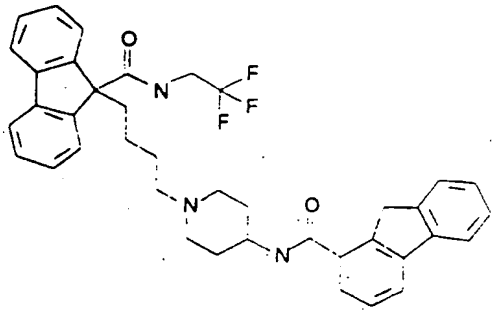

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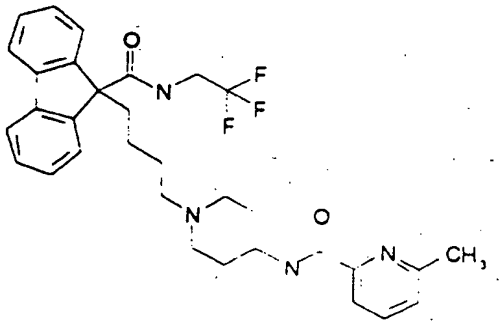

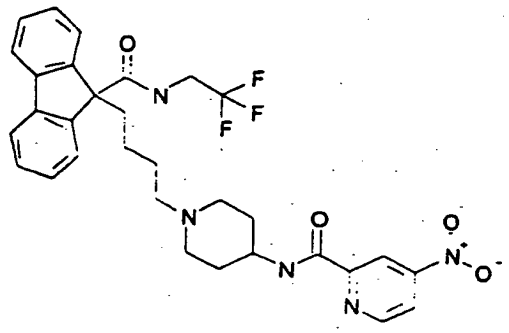

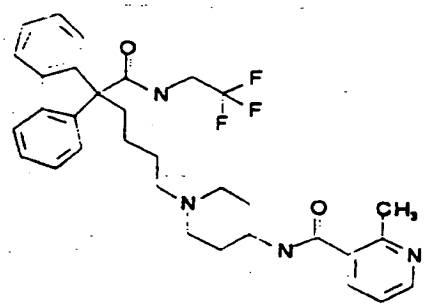

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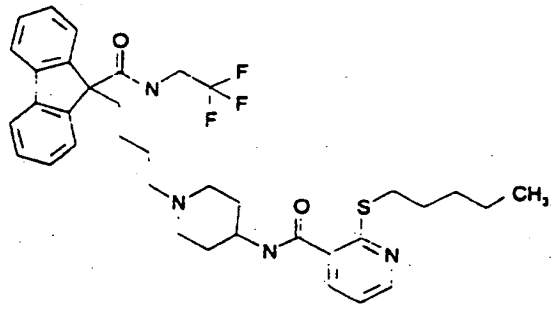

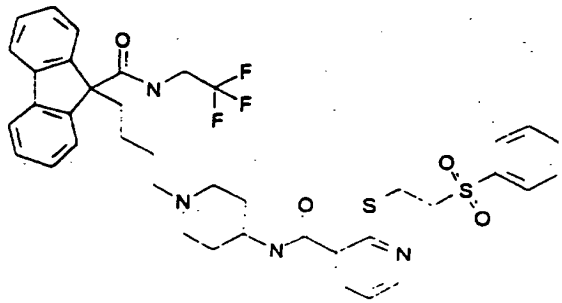

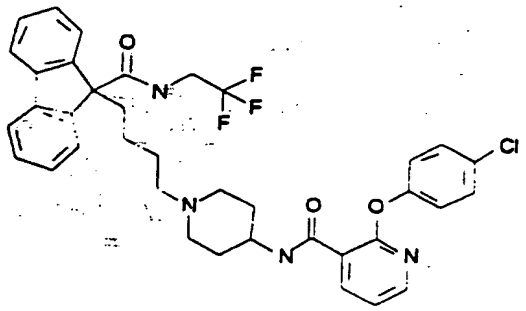

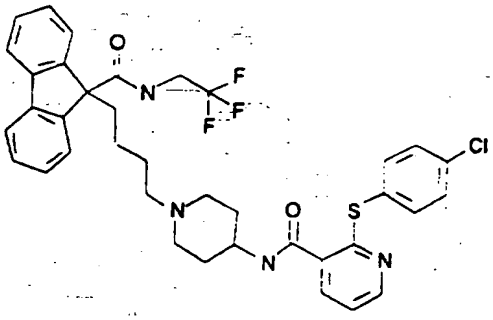

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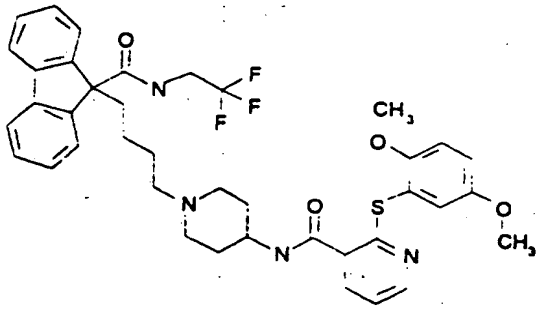

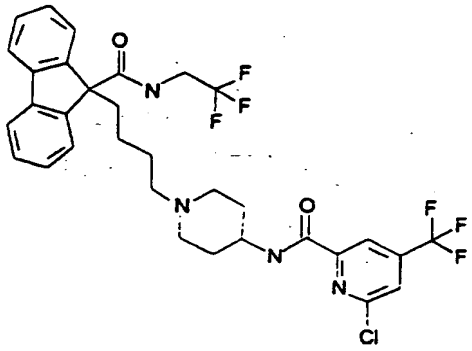

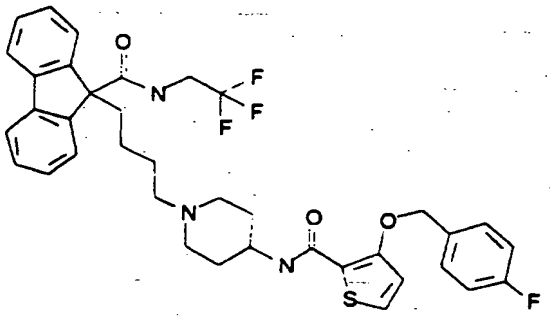

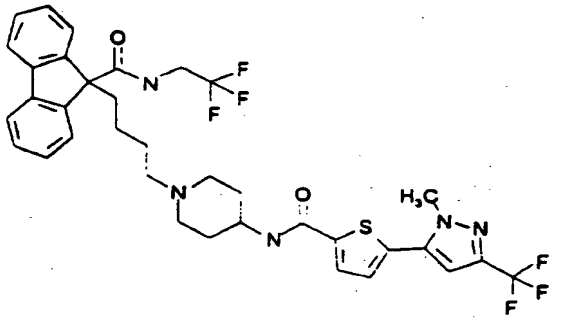

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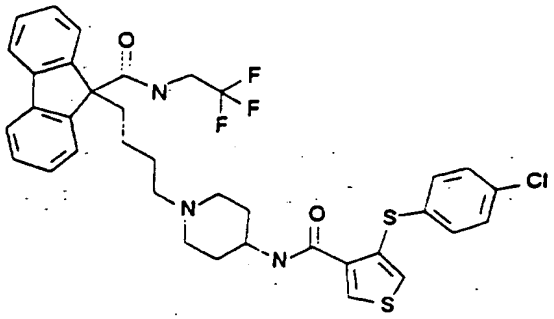

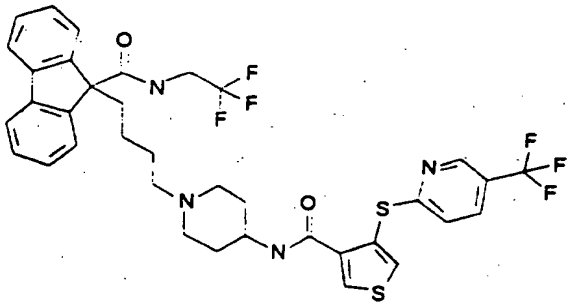

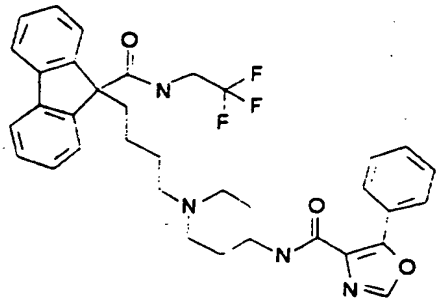

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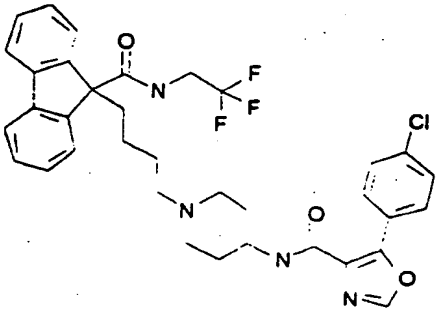

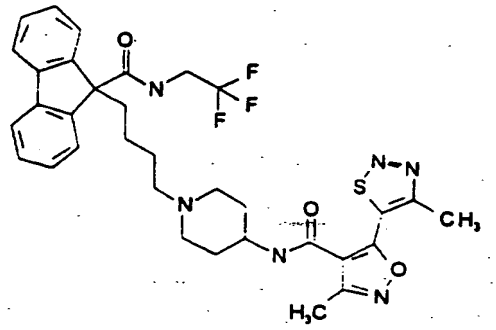

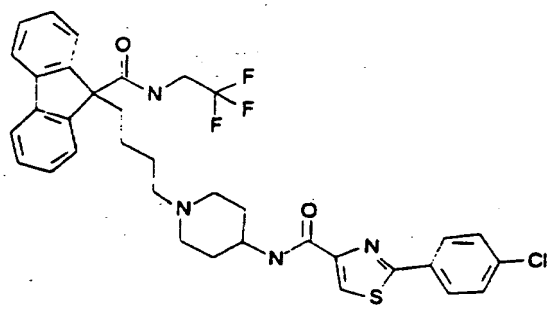

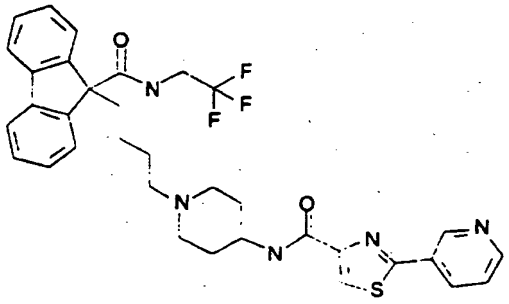

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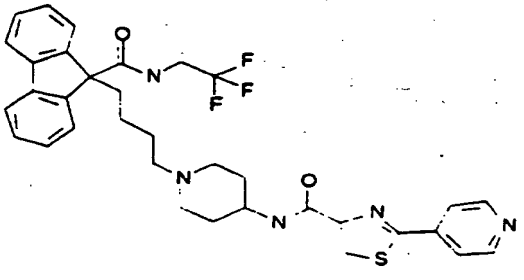

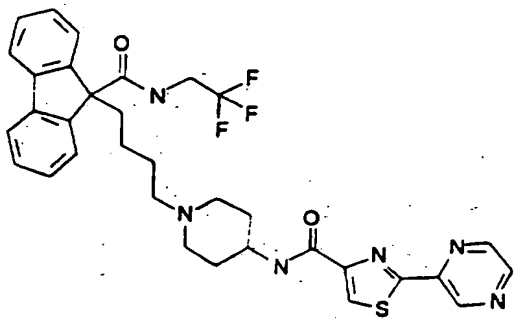

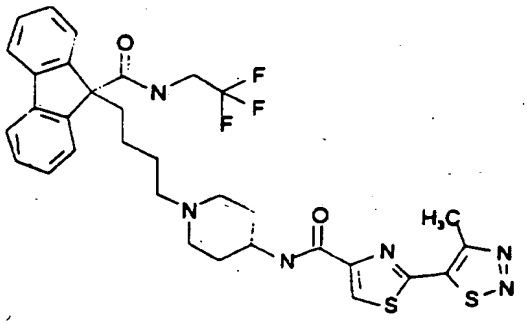

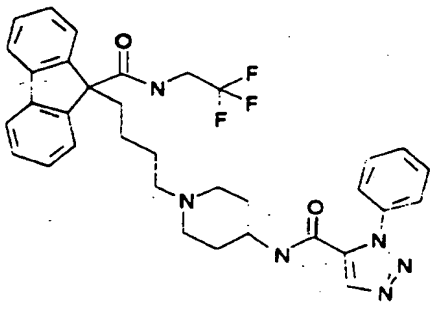

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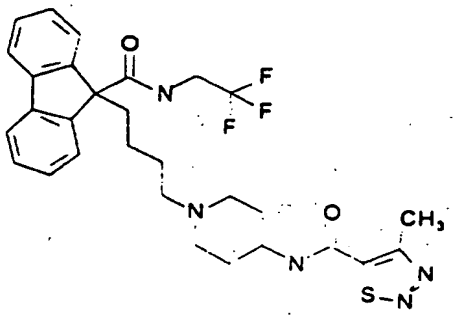

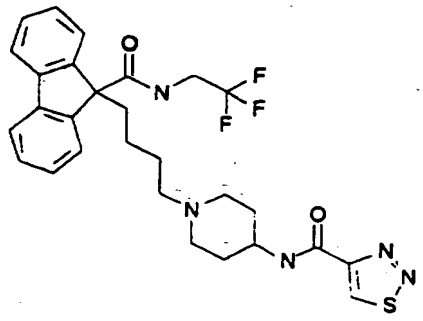

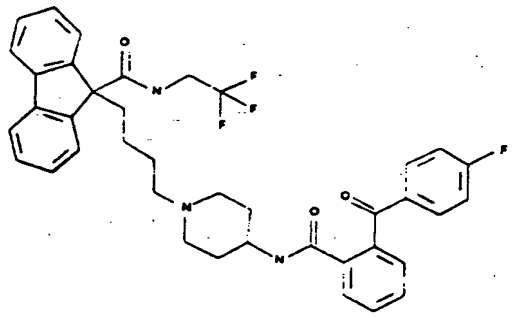

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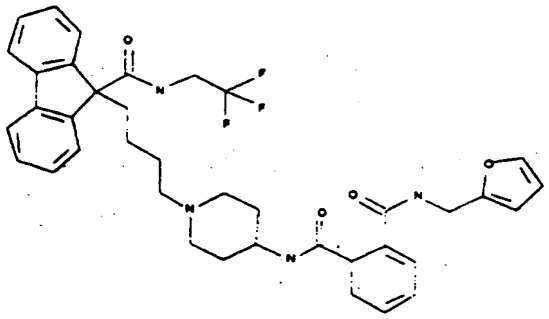

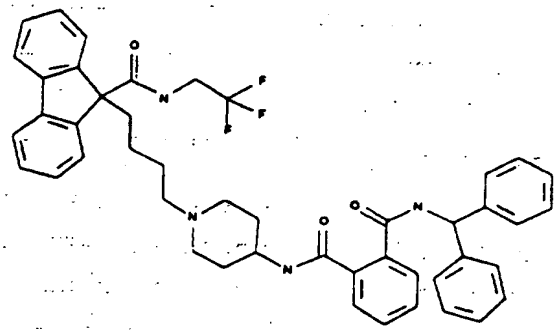

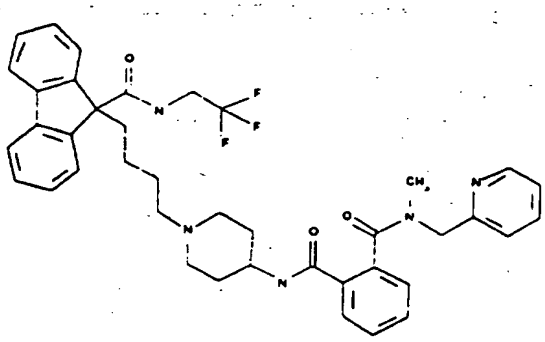

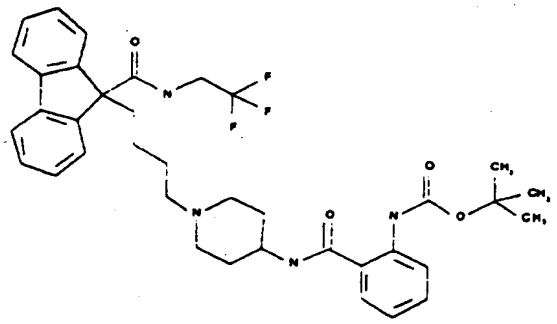

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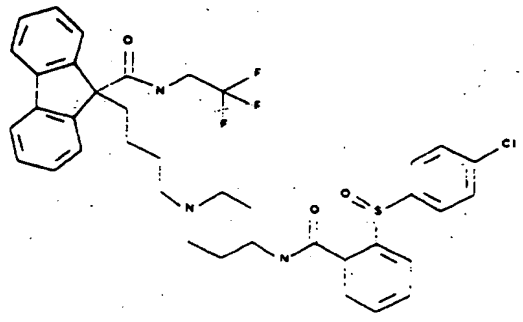

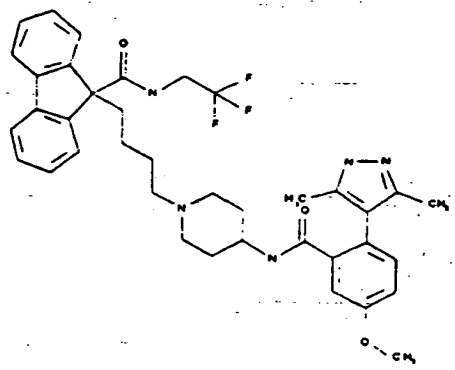

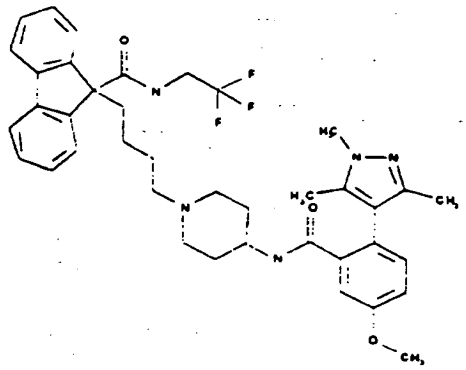

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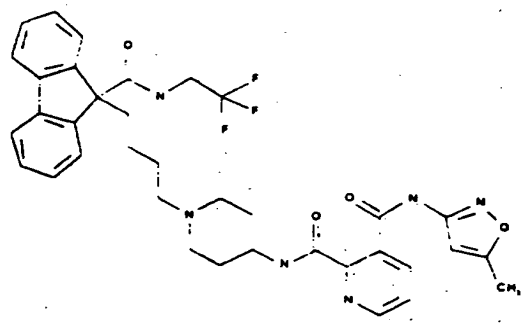

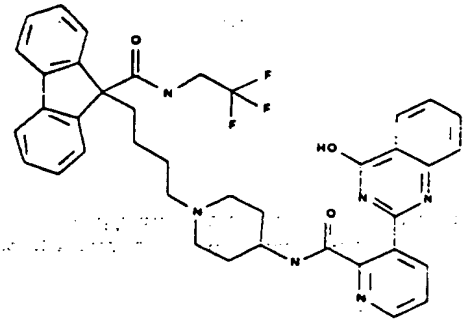

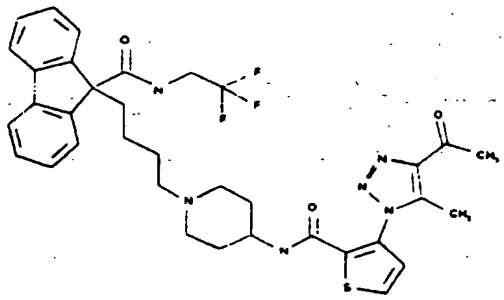

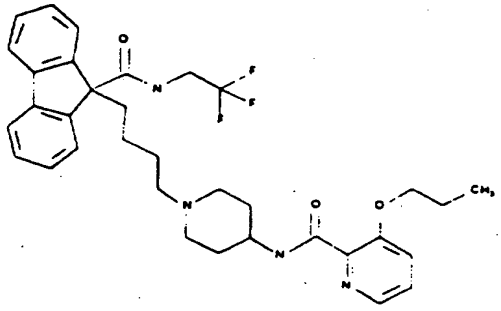

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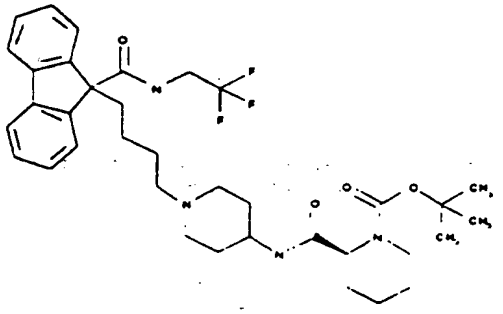
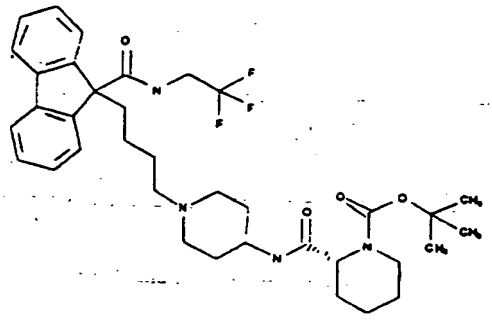
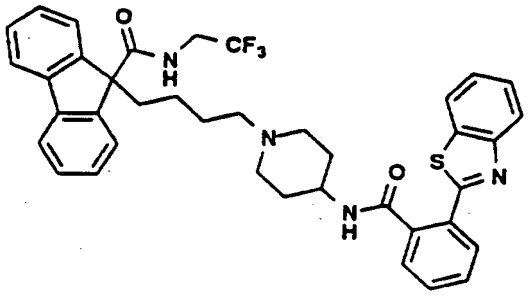
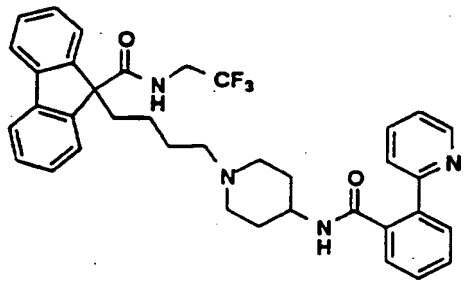


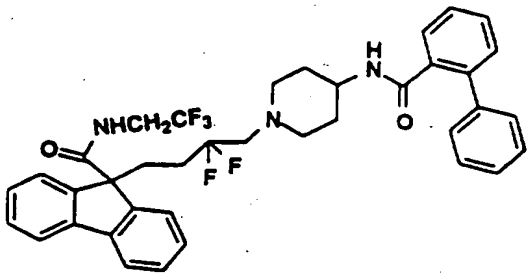


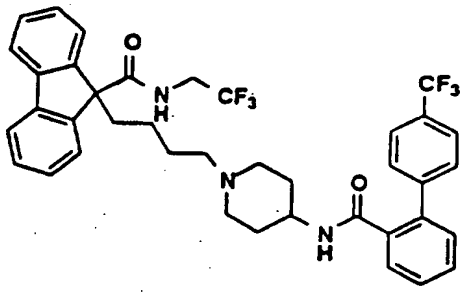
the monohydrochloride thereof, the dihydrochloride thereof or the pharmaceutically acceptable salt thereof.

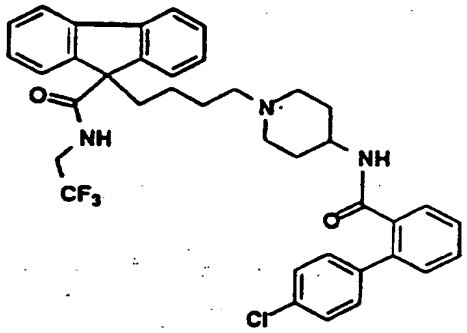
22. The compound as defined in Claim 14 which is

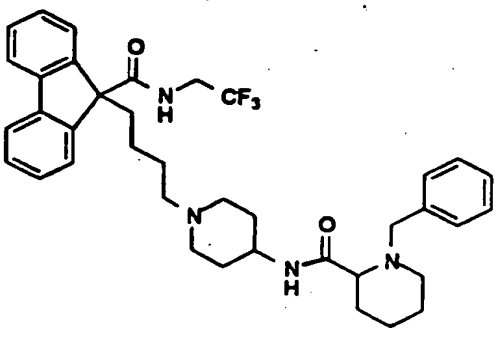


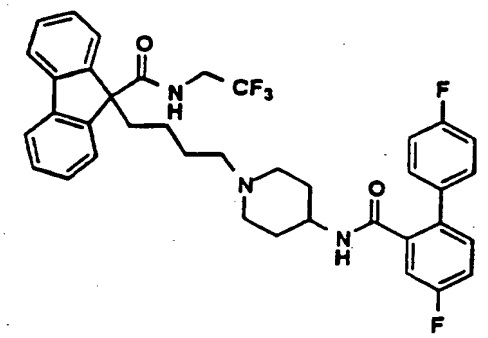


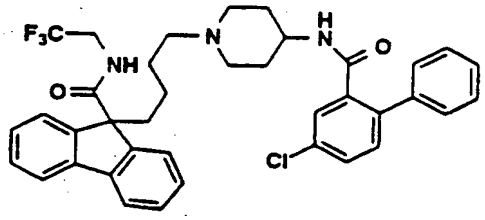


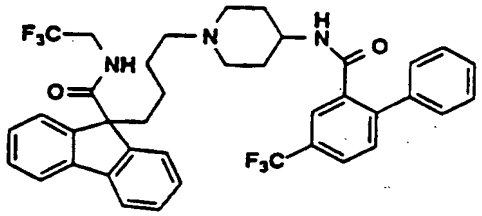


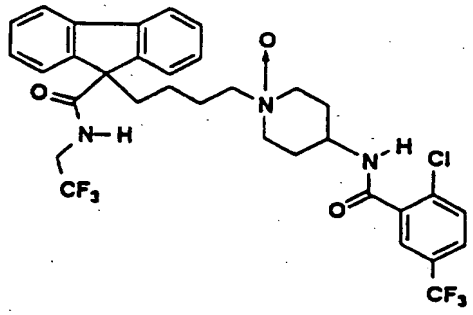


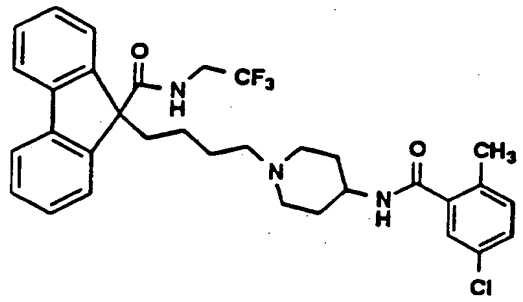


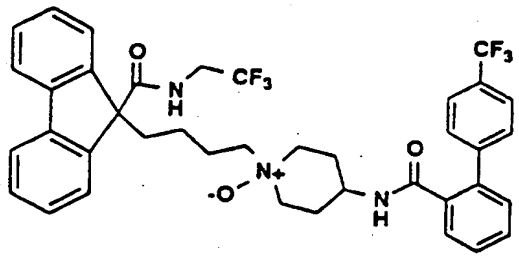


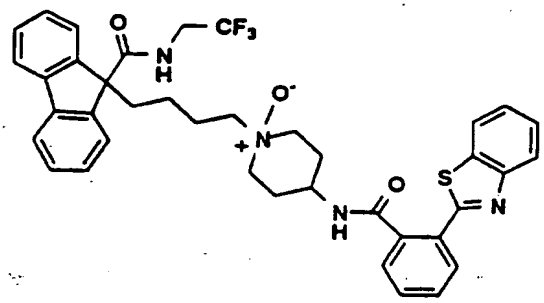












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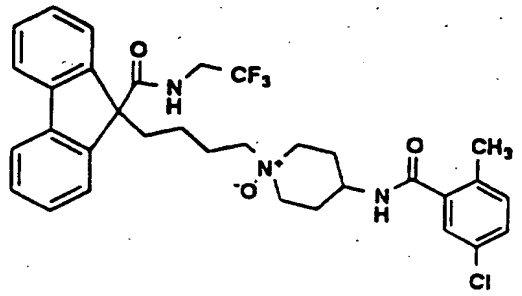

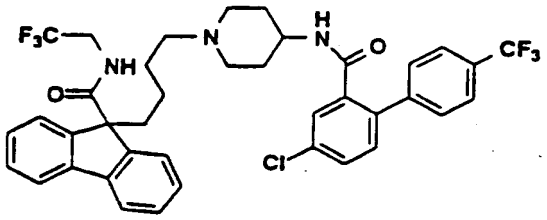

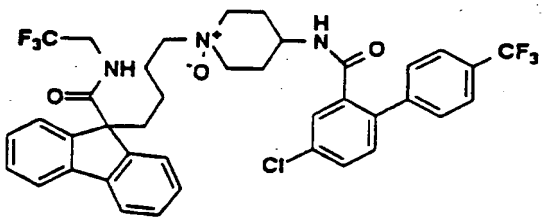

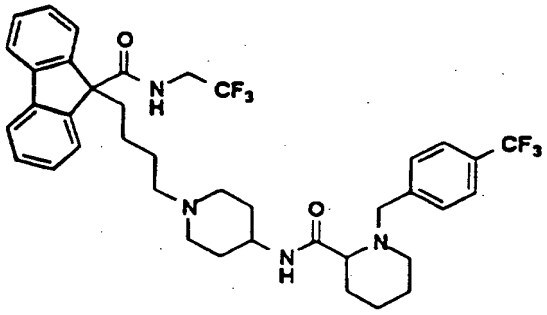

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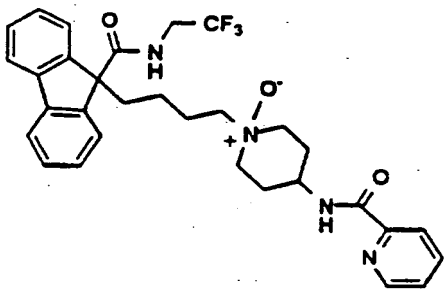

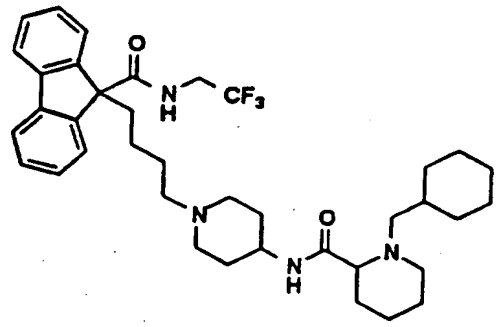

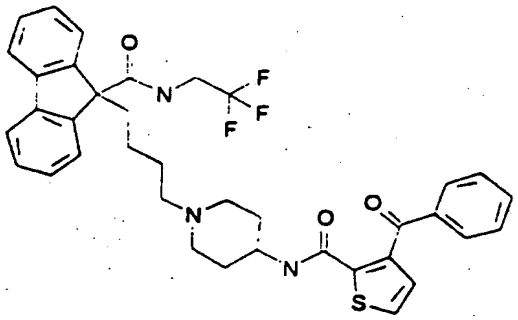

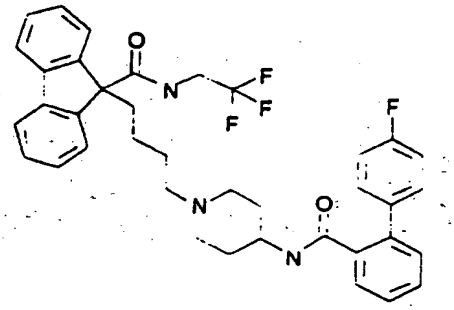

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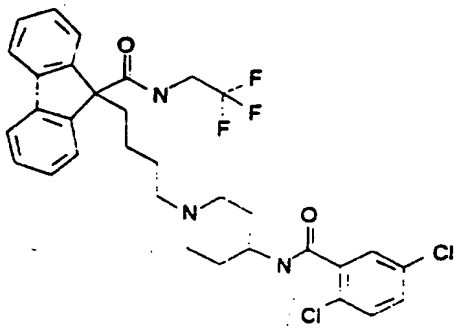
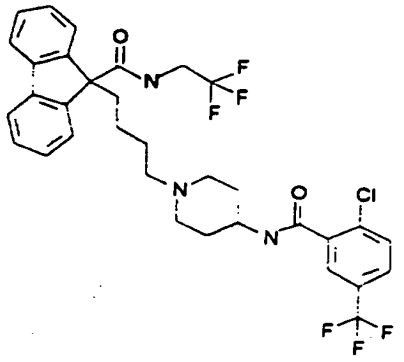
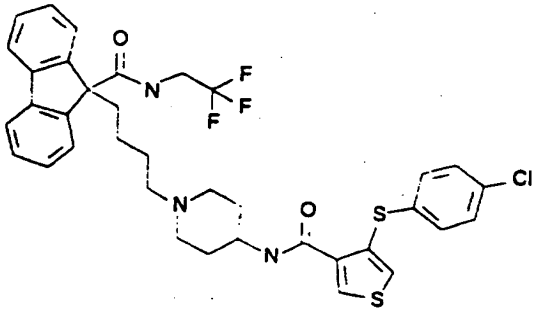
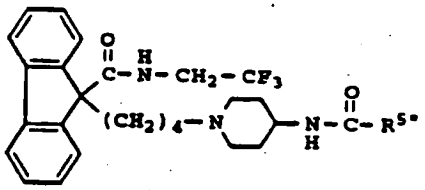






the monohydrochloride thereof, the dihydrochloride thereof or other pharmaceutically acceptable salt thereof.

23. A compound having the structure



including the piperidine N-oxide thereof or a pharmaceutically acceptable salt thereof,

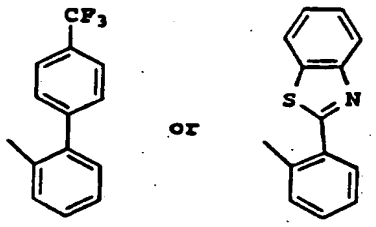
R^{5*} is heteroaryl, aryl, heterocycloalkyl or cycloalkyl, each R^{5*} group being optionally

substituted with 1, 2, 3 or 4 substituents which may be the same or different.

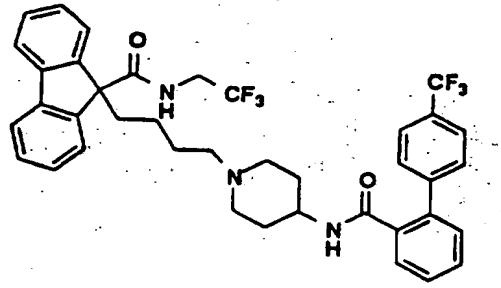
24. The compound as defined in Claim 23 wherein the substituent on R^{5*} is adjacent to the carbon attached to the $\overset{O}{\overset{\|}{C}}$ group.

25. The compound as defined in Claim 23 wherein R^{5*} is phenyl substituted with haloalkyl-phenyl or heteroaryl.

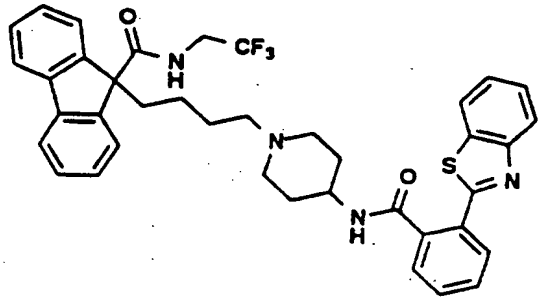
26. The compound as defined in Claim 25 wherein R^{5*} is



27. The compound as defined in Claim 23 which is



or



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00824

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :Please See Extra Sheet.
US CL :546/141, 194, 196, 197, 198, 199, 200, 203, 205; 514/309, 323
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 546/141, 194, 196, 197, 198, 199, 200, 203, 205; 514/309, 323

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US, A, 3,910,931 (CAVALLA ET AL.) 07 October 1975, see column 1, lines 11 to 51.	1, 3, 4, 12
X	US, A, 5,189,045 (PEGLION ET AL.) 23 February 1993, see column 1, line 35 to column 2, line 68 and column 27, line 54.	1, 3, 4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
08 MAY 1996	13.05.96
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer KING L. WONG Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00824

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US96/00824

A. CLASSIFICATION OF SUBJECT MATTER:
IPC (6):

C07D 401/04, 401/06, 401/12, 405/04, 405/06, 405/12, 409/04, 409/06, 409/12, 211/58; A61K 31/445

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claims 1, 2, 5, 6 and 11-13, drawn to compounds and methods wherein the structure is either one of the first two formulae in claim 1 and X is -CHR8- or -C(O)-.

Group II, claims 1, 2, 5, 6 and 11-13, drawn to compounds and methods wherein the structure is either one of the first two formulae in claim 1 and X is -CHR9-CHR10- or -CR9=CR10-.

Group III, claims 1 and 3-27, drawn to compounds and methods wherein the structure is either one of the last two formulae in claim 1.

The inventions listed as Groups I-III do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the common structure is not a significant structural element of the molecule and they are not art recognized equivalents (see Examples 19 and 20 of the PCT Administrative Instructions, Annex B, Part 2).